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PATENT APPLICATION

QUINAZOLINES AS MMP-13 INHIBITORS

Field of the invention.

The present invention relates to novel substituted quinazolines which are useful for preparing medicinal products for treating complaints involving a therapy with a matrix metalloprotease-13 (MMP-13) inhibitor. These medicinal products are useful in particular for treating certain inflammatory conditions such as rheumatoid arthritis or osteoarthritis, as well as certain proliferative conditions such as cancers.

Technological background of the invention.

Matrix metalloproteases (MMPs) are enzymes which are involved in the renewal of extracellular matrix tissue, such as cartilage, tendons and joints. MMPs bring about the destruction of the extracellular matrix tissue, which is compensated for, in a non-pathological physiological state, by its simultaneous regeneration.

Under normal physiological conditions, the activity of these extremely aggressive peptidases is controlled by specialized proteins which inhibit MMPs, such as the tissue inhibitors of metalloprotease (TIMPs).

Local equilibrium of the activities of MMPs and of TIMPs is critical for the renewal of the extracellular matrix. Modifications of this equilibrium which result in an excess of active MMPs, relative to their inhibitor, induce a pathological destruction of cartilage, which is observed in particular in rheumatoid arthritis and in osteoarthritis.

In pathological situations, an irreversible degradation of articular cartilage takes place, as is the case in rheumatic diseases such as rheumatoid arthritis or osteoarthritis. In these pathologies, the cartilage degradation process predominates, leading to a destruction of the tissue and resulting in a loss of function.

At least twenty different matrix metalloproteases have been identified to date and are subdivided into four groups, the collagenases, the gelatinases, the stromelysins and the membrane-type MMPs (MT-MMPs), respectively.

Matrix metalloprotease-13 (MMP-13) is a collagenase-type MMP which constitutes the predominant collagenase observed during osteoarthritis, in the course of which pathology the chondrocyte directs the destruction of cartilage.

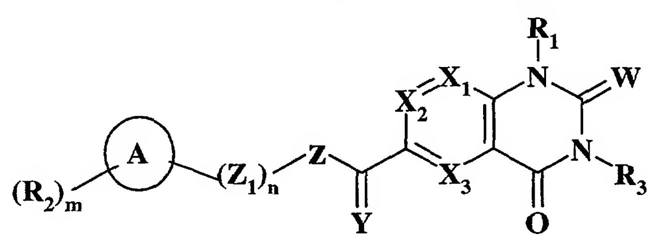
There is a need in the prior art for novel MMP inhibitors, more particularly for MMP-13 inhibitors, in order to prevent and/or correct the imbalance in the renewal of extracellular matrix tissue, such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary diseases (COPD), age-related macular degeneration (ARMD) and cancer.

MMP-inhibitor compounds are known. Most of these MMP-inhibitors are not selective for a single MMP, such as those described by Montana and Baxter (2000) or by Clark et al. (2000).

There is also a need in the prior art for novel inhibitors that are active on matrix metalloprotease-13, in order to enrich the therapeutic arsenal that can be used for treating pathologies associated with the destruction of the extracellular matrix and with cancer.

Summary of the invention

The invention relates to a substituted quinazoline of formula (I):



(I)

in which:

R_1 represents a group selected from :

- hydrogen, amino,
- (C_1-C_6)alkyl, (C_3-C_6)alkenyl, (C_3-C_6)alkynyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, heterocycle, and 3- to 6-membered cycloalkyl(C_1-C_6)alkyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, (C_1-C_6)alkyl, cyano, halo(C_1-C_6)alkyl, C(=O)OR_4, OR_4 and SR_4, in which R_4 represents hydrogen or (C_1-C_6)alkyl,

W represents an oxygen atom, a sulphur atom, or a group =N-R', in which R' represents $(C_1\text{-}C_6)$alkyl, hydroxyl, or cyano,

X_1, X_2 and **X_3** represent, independently of each other, a nitrogen atom or a group -C-R_6 in which R_6 represents a group selected from hydrogen, $(C_1\text{-}C_6)$alkyl, amino, mono$(C_1\text{-}C_6)$alkylamino, di$(C_1\text{-}C_6)$alkylamino, hydroxyl, $(C_1\text{-}C_6)$alkoxy, and halogen,
with the proviso that not more than two of the groups X_1, X_2 and X_3 simultaneously represent a nitrogen atom,

Y represents a group selected from oxygen atom, sulphur atom, -NH, and -N$(C_1\text{-}C_6)$alkyl,

Z represents:

- an oxygen atom, a sulphur atom,
- or a group $-NR_7$ in which R_7 represents a group selected from hydrogen, $(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkyl, cycloalkyl, aryl, and heteroaryl, and
- when Y is an oxygen atom, a sulphur atom, or a group -N$(C_1\text{-}C_6)$alkyl, Z optionally represents a carbon atom which is unsubstituted or substituted with a $(C_1\text{-}C_6)$alkyl, an aryl, an aryl$(C_1\text{-}C_6)$alkyl, an aromatic or non-aromatic heterocycle or a cycloalkyl,

n is an integer from 1 to 8 inclusive,

Z_1 represents $-CR_8R_9$ wherein R_8 and R_9, independently of each other, represent a group selected from hydrogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, halogen, amino, OR_4, SR_4 or $C(=O)OR_4$ in which R_4 represents a hydrogen or $(C_1\text{-}C_6)$alkyl, and

- when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one or more multiple bonds,
- and/or one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a nitrogen atom which is unsubstituted or substituted with a $(C_1\text{-}C_6)$alkyl,

- and when one of the carbon atoms in the hydrocarbon chain Z_1 is replaced with a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, then the group –C(=Y)-Z- optionally may be absent in the general formula (I),

A represents a group selected from :

- aromatic or non-aromatic, 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and
- bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

m is an integer from 0 to 7 inclusive,

the group(s) R_2, which may be identical or different, is (are) selected from $(C_1\text{-}C_6)$alkyl, halogen, -CN, NO_2, SCF_3, $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, $-(CH_2)_kSO_2NR_{10}R_{11}$, $-X_5(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$, $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$, $-(CH_2)_kC(=O)NR_{10}R_{11}$, and $-X_4-R_{12}$ in which:

- X_5 represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen atoms, and nitrogen substituted by hydrogen or $(C_1\text{-}C_6)$alkyl,

- k is an integer from 0 to 3 inclusive,

- R_{10} and R_{11}, which may be identical or different, are selected from hydrogen and $(C_1\text{-}C_6)$alkyl,

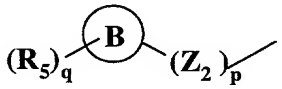
- X_4 represents a group selected from single bond, $-CH_2-$, oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or $(C_1\text{-}C_6)$alkyl group,

- R_{12} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring which is unsubstituted or substituted with one or more groups, which

may be identical or different, selected from (C_1-C_6)alkyl, halogen, hydroxyl and amino, and when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur;

R_3 represents a group selected from:

- hydrogen,
- (C_1-C_6)alkyl, (C_3-C_6)alkenyl, (C_3-C_6)alkynyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, cyano, halo(C_1-C_6)alkyl, cycloalkyl, -C(=O)$NR_{10}R_{11}$, -C(=O)OR_{10}, OR_{10}, and SR_{10}, in which R_{10} and R_{11}, which may be identical or different, represent hydrogen or (C_1-C_6)alkyl,
- and the group of formula :



✓ in which p is an integer from 0 to 8 inclusive,

✓ Z_2 represents -$CR_{13}R_{14}$ wherein R_{13} and R_{14}, independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl, phenyl, halo(C_1-C_6)alkyl, halogen, amino, OR_4, SR_4 and -C(=O)OR_4 in which R_4 represents hydrogen or (C_1-C_6)alkyl, and

- when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one or more multiple bonds,
- and/or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6)alkyl, or a carbonyl group,

✓ B represents a group selected from:

- an aromatic or non-aromatic 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and

- a bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

✓ q is an integer from 0 to 7 inclusive,

✓ the group(s) R_5, which may be identical or different, is (are) selected from $(C_1\text{-}C_6)$alkyl, halogen, CN, NO_2, CF_3, OCF_3, $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2\text{-}N(R_{15})\text{-}(CH_2)_{k2}\text{-}NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O\text{-}(CH_2)_{k2}\text{-}NR_{15}R_{16}$, $-C(=O)O\text{-}(CH_2)_{k2}\text{-}C(=O)OR_{18}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, $-(CH_2)_kC(=O)NR_{15}R_{16}$, $-R_{19}\text{-}C(=O)OR_{15}$, $-X_6\text{-}R_{20}$, and $-C(=O)\text{-}R_{21}\text{-}NR_{15}R_{16}$ in which :

- X_7 represents a group selected from oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by a hydrogen atom or a $(C_1\text{-}C_6)$alkyl group,

- k is an integer from 0 to 3 inclusive,

- k1 is an integer from 0 to 2 inclusive,

- k2 is an integer from 1 to 4 inclusive,

- R_{15}, R_{16} and R_{17}, which may be identical or different, are selected from hydrogen and $(C_1\text{-}C_6)$alkyl,

- R_{18} represents a group selected from $(C_1\text{-}C_6)$alkyl, $-R_{21}\text{-}NR_{15}R_{16}$, $-R_{21}\text{-}NR_{15}\text{-}C(=O)\text{-}R_{21}\text{-}NR_{16}R_{17}$, and $-C(=O)O\text{-}R_{21}\text{-}NR_{15}R_{16}$ in which R_{21} represents a linear or branched $(C_1\text{-}C_6)$alkylene group, and R_{15}, R_{16} and R_{17} are as defined hereinbefore,

- R_{19} represents a $(C_3$-$C_6)$cycloalkyl group,

- X_6 represents a group selected from single bond, $-CH_2-$, oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or $(C_1$-$C_6)$alkyl group,

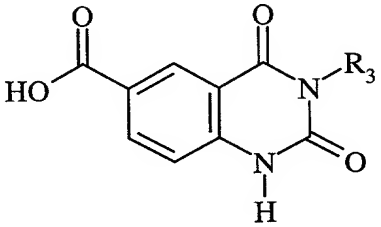
- R_{20} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from $(C_1$-$C_6)$alkyl, halogen, hydroxyl, oxo, cyano, tetrazole, amino, and $-C(=O)OR_4$ wherein R_4 represents hydrogen or $(C_1$-$C_6)$alkyl, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

with the proviso that when X_1 represents a nitrogen atom, X_2 cannot represent a carbon atom substituted with a methyl group or with $NH-CH_3$,

optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

The compounds of the present invention are useful as inhibitors, in particular as selective inhibitors, of the enzyme matrix metalloprotease-13 (MMP-13).

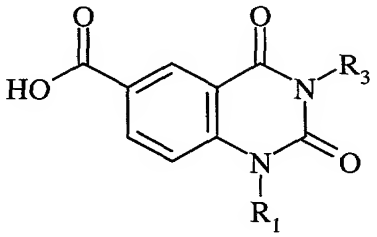
The invention also relates to compounds used mainly as intermediates for the synthesis of the compounds of formula (I). These intermediate compounds have the general formula (III) below:



(III)

in which R_3 has the same meaning as defined for the compound of formula (I).

The invention also relates to compounds used mainly as intermediates for the synthesis of the compound of formula (I), which have the general formula (IV) below:



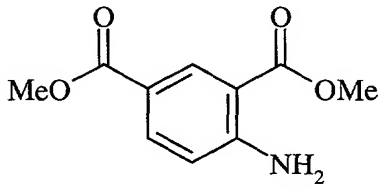
(IV)

in which R_1 et R_3 have the same meaning as for a compound of formula (I).

The invention also relates to a process for manufacturing the compound of formula (I) in which:

- R_2, R_3, Z_1, A, n and m are as defined in the compound of general formula (I),
- X_1, X_2, X_3 are each a group -C-R_6 in which R_6 represents a hydrogen atom,
- Y is O,
- Z is -N-R_7 in which R_7 is as defined in the compound of general formula (I),
- and W is O.

This process is characterized in that it comprises the reaction of a compound of formula (II):



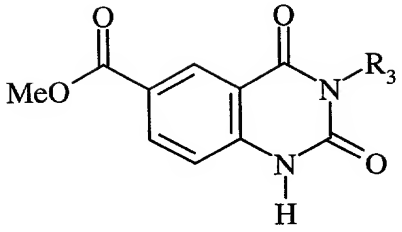
(II)

with pyridine and the compound of general formula (V):

$$O=C=N-R_3 \qquad \textbf{(V)}$$

in which R_3 is as defined above for the compound of formula (I),

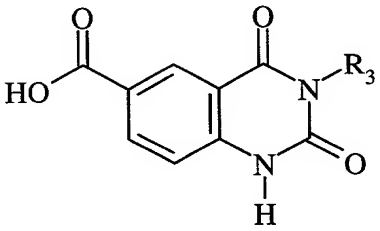
to give the compound of general formula (VI):



(VI)

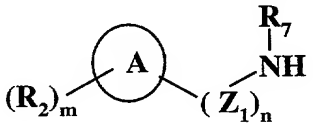
in which R_3 is as defined hereinbefore,

followed by reacting the compound of general formula (VI) in the presence of LiOH to give the compound of general formula (III) in which R_3 is as defined above.



(III)

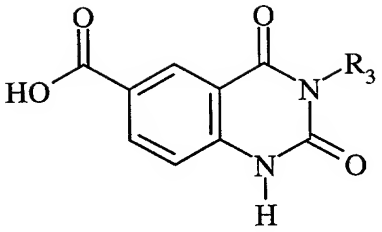
In a subsequent step of the synthetic process, the compound of general formula (III) obtained above is reacted, in the presence of an acid activator such as O-[(ethoxycarbonyl)cyanomethylenamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU) with the compound of general formula (VII):



(VII)

in which R_7 is selected from hydrogen, $(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2, Z_1, n and m are as defined above for the compound of formula (I), to give the compound of general formula (I) in which R_1 represents hydrogen, X_1, X_2 and X_3 are each -C-R_6 in which R_6 represents hydrogen atom, Y is O, Z is N-R_7, W is O, , and A, R_2, Z_1, n and m are as defined hereinbefore.

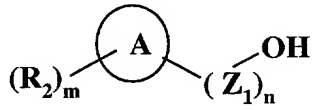
In particular, when W is O, Y is O and Z is O, the compounds of formula (I) corresponding to this definition may be obtained by reacting a compound of general formula (III):



(III)

in which R_3 is as defined in the compound of general formula (I),

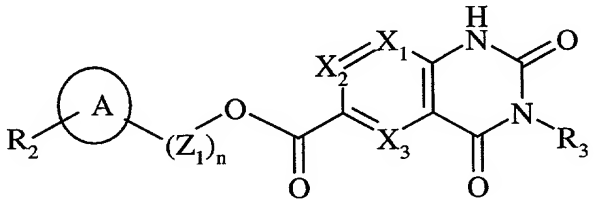
with a compound of general formula (XVI):



(XVI)

in which Z_1, A, R_2, n and m are as defined in the compound of general formula (I),

to give a compound of general formula (XVII):



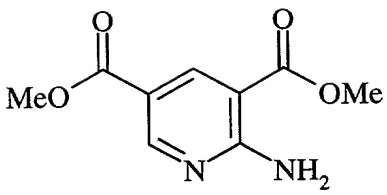
(XVII)

in which A, R_2, R_3, Z_1 m and n are as defined for the compound of general formula (I), and X_1, X_2, and X_3 are each -C-R_6 in which R_6 represents hydrogen atom,

followed by reacting the compound of formula (XVII), in presence of a base, with the compound of general formula (VIII), X-R_1, in which R_1 is as defined for the compound of formula (I) and X is a leaving group such as halogen,

to give the compound of general formula (I) in which X_1, X_2 and X_3 are each –C-R_6 in which R_6 is as defined hereinbefore, W is O, Y is O, Z is O, and R_1, R_2, R_3, Z_1, A, n and m are as defined hereinbefore.

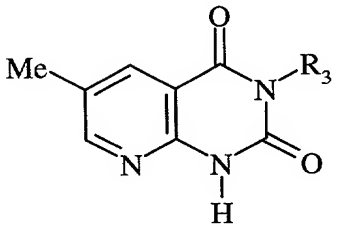
In particular, when X_2 and X_3 are each –C-R_6 in which R_6 represents hydrogen atom , X_1 is N, Z is O and Y is O, the compounds of formula (I) corresponding to this definition may be obtained by reacting a compound of general formula (XIX):



(XIX)

with pyridine and a compound of general formula O=C=N-R_3 (V) in which R_3 is as defined in the compound of formula (I),

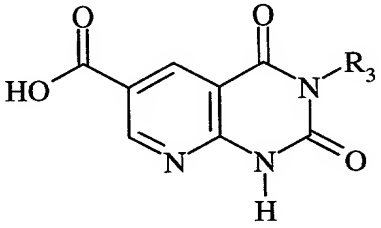
to give a compound of general formula (XX):



(XX)

in which R_3 is as defined hereinbefore,

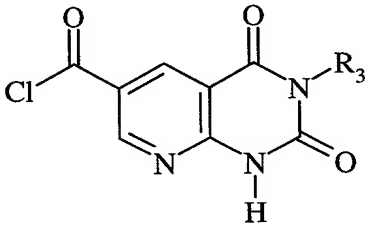
followed by reacting the compound of general formula (XX) in the presence of $KMnO_4$ to give the compound of general formula (XXI):



(XXI)

in which R_3 is as defined hereinbefore,

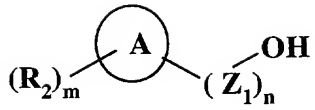
followed by reacting a compound of general formula (XXI) in the presence of $SOCl_2$ and $CHCl_3$ to give the compound of general formula (XXII):



(XXII)

in which R_3 is as defined hereinbefore,

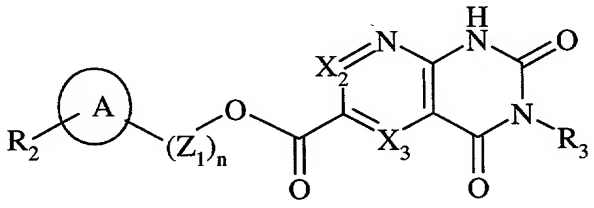
followed by reacting the compound of formula (XXII) with the compound of general formula (XVI):



(XVI)

in which A, R_2, Z_1, n and m are as defined in the compound of formula (I),

to give the compound of general formula (I):



(XXIV)

in which A, R_2, R_3, Z_1 m and n are as defined hereinbefore, X_2 and X_3 are each -C-R_6 in which R_6 is as defined hereinbefore, and R_3 are as defined for the compound of general formula (I).

The invention also relates to a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient.

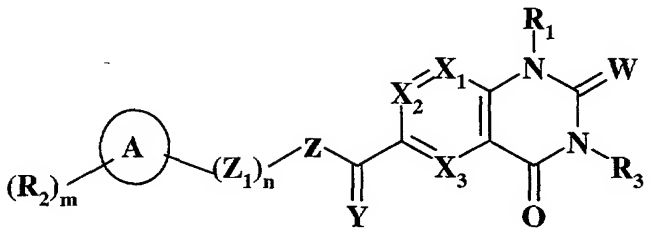
The invention also relates to the use of a compound of formula (I) for the preparation of a medicinal product intended for treating a disease or complaint involving therapy by inhibition of matrix metalloprotease, and more particularly of type-13 matrix metalloprotease (MMP-13).

The invention also relates to a method for treating a disease or complaint involving a therapy by inhibition of matrix metalloprotease, and more particularly MMP-13, the said method comprising the administration of an effective amount of a compound of formula (I) to a patient.

Detailed description of the invention

The Applicant has identified according to the invention novel compounds that are matrix metalloprotease inhibitors, and more specifically novel compounds that are MMP-13 inhibitors.

One subject of the invention is thus a substituted quinazoline of formula (I):



(I)

in which R_1, R_2, R_3, X_1, X_2, X_3, W, Y, Z, Z_1, n and m are as defined hereinbefore in the compound of general formula (I),

optionally the racemic fo rms thereof, isomers forms thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

The invention relates particularly to the compounds of general formula (I) in which:

- R_1 represents hydrogen, $(C_1$-$C_6)$alkyl, aryl$(C_1$-$C_6)$alkyl or 3- to 6-membered cycloalkyl$(C_1$-$C_6)$alkyl,
- W represents an oxygen atom or a sulphur atom,
- X_1 represents a nitrogen atom or -C-R_6 in which R_6 represents a hydrogen atom,
- X_2 and X_3 represent each -C-R_6 in which R_6 represents a hydrogen atom,
- Y represents an oxygen atom,
- Z represents an oxygen atom or -NR_7 in which R_7 represents a hydrogen atom.

The invention also relates to the compounds of general formula (I) in which:

- n is an integer from 1 to 6 inclusive,

- Z_1 represents –CR_8R_9 wherein R_8 represents a hydrogen atom and R_9 represents a hydrogen atom or a methyl group, and

- when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains a double bond,

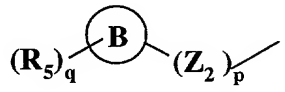
- or, one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, or a sulphur atom which is unsubstituted or substituted with one or two oxygens,

- A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, piperidyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzofurazanyl, 2,1,3-benzothiadiazolyl, and indolyl,

- m is an integer from 0 to 7 inclusive,

- the group(s) R_2, which may be identical or different, is (are) selected from $(C_1\text{-}C_6)$alkyl, halogen, -CN, $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, $-SO_2R_{10}$, $-(CH_2)_kSO_2NR_{10}R_{11}$, $-X_5(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$, $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$, $-(CH_2)_kC(=O)NR_{10}R_{11}$, and $-X_4\text{-}R_{12}$ in which:
  - ✓ X_5 represents O, S or NH,
  - ✓ k is an integer from 0 to 3 inclusive,
  - ✓ R_{10} and R_{11}, identical or different, are selected from hydrogen and $(C_1\text{-}C_6)$alkyl,
  - ✓ X_4 represents $-CH_2-$, or an oxygen atom,
  - ✓ R_{12} represents a phenyl group which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from $(C_1\text{-}C_6)$alkyl, halogen, hydroxyl and amino.

The invention also relates to the compounds of general formula (I) in which R_3 represents hydrogen, $(C_1\text{-}C_6)$alkyl or the group of formula:



- ✓ in which p is an integer from 0 to 3 inclusive,

- ✓ Z_2 represents $-CR_{13}R_{14}$ wherein R_{13} and R_{14}, independently of each other, represent a group selected from hydrogen, methyl, or phenyl, and
  - when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one double bond,

- or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6)alkyl, or a carbonyl group,

✓ B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,

✓ q is an integer from 0 to 3 inclusive,

✓ the group(s) R_5, which may be identical or different, is (are) selected from (C_1-C_6)alkyl, halogen, CN, NO_2, CF_3, OCF_3, $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, and $-(CH_2)_kC(=O)NR_{15}R_{16}$ in which :

- X_7 is S, O or NH,
- k is an integer from 0 to 3 inclusive,
- k1 is an integer from 0 to 2 inclusive,
- k2 is an integer from 1 to 4 inclusive,
- R_{15}, R_{16} and R_{17}, identical or different, are selected from hydrogen and (C_1-C_6)alkyl,

The invention relates more particularly to the compounds of general formula (I) in which:

R_1 represents a group selected from:

- hydrogen, amino,
- (C_1-C_6)alkyl, (C_3-C_6)alkenyl, (C_3-C_6)alkynyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, heterocycle, and 3- to 6-membered cycloalkyl(C_1-C_6)alkyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, (C_1-

C_6)alkyl, cyano, halo(C_1-C_6)alkyl, C(=O)OR_4, OR_4 and SR_4, in which R_4 represents hydrogen or (C_1-C_6)alkyl,

W represents an oxygen atom, a sulphur atom, or a group =N-R', in which R' represents (C_1-C_6)alkyl, hydroxyl, or cyano,

X_1 represents a nitrogen atom or a group -C-R_6 in which R_6 represents hydrogen atom, X_2 and X_3 represent, independently of each other, a group -C-R_6 in which R_6 represents a group selected from hydrogen, (C_1-C_6)alkyl, amino, hydroxyl and halogen,

Y represents an oxygen atom,

Z represents an oxygen atom, or a group –NR_7 in which R_7 represents a group selected from hydrogen, and (C_1-C_6)alkyl,

n is an integer from 1 to 6 inclusive,

Z_1 represents –CR_8R_9 wherein R_8 and R_9, independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl and hydroxyl, and

- when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one or more multiple bonds,
- or one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6)alkyl,

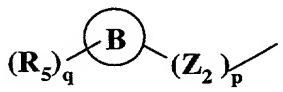
A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzofurazanyl, 2,1,3-benzothiadiazolyl, and indolyl,

m is an integer from 0 to 3 inclusive,

the group(s) R_2, which may be identical or different, is (are) selected from $(C_1\text{-}C_6)$alkyl, halogen, -CN, $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, $-SO_2R_{10}$, $-(CH_2)_kSO_2NR_{10}R_{11}$, $-X_5(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$, $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$, $-(CH_2)_kC(=O)NR_{10}R_{11}$, and $-X_4\text{-}R_{12}$ in which:

- X_5 represents O, S or NH,
- k is an integer from 0 to 3 inclusive,
- R_{10} and R_{11}, which may be identical or different, are selected from hydrogen and $(C_1\text{-}C_6)$alkyl,
- X_4 represents $-CH_2-$, or an oxygen atom,
- R_{12} represents phenyl which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from $(C_1\text{-}C_6)$alkyl, halogen, and hydroxyl,

R_3 represents a group selected from hydrogen, $(C_1\text{-}C_6)$alkyl, and the group of formula :



- ✓ in which p is an integer from 0 to 6 inclusive,
- ✓ Z_2 represents $-CR_{13}R_{14}$ wherein R_{13} and R_{14}, independently of each other, represent a group selected from hydrogen, $(C_1\text{-}C_6)$alkyl, and hydroxy, and
  - when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one or more multiple bonds,
  - or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a $(C_1\text{-}C_6)$alkyl,
- ✓ B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,
- ✓ q is an integer from 0 to 3 inclusive,

- ✓ the group(s) R_5, which may be identical or different, is (are) selected from $(C_1\text{-}C_6)$alkyl, halogen, CN, NO_2, CF_3, OCF_3, $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2\text{-}N(R_{15})\text{-}(CH_2)_{k2}\text{-}NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O\text{-}(CH_2)_{k2}\text{-}NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, $-(CH_2)_kC(=O)NR_{15}R_{16}$, and $-X_6\text{-}R_{20}$ in which :
  - X_7 is S, O or NH,
  - k is an integer from 0 to 3 inclusive,
  - k1 is an integer from 0 to 2 inclusive,
  - k2 is an integer from 1 to 4 inclusive,
  - R_{15}, R_{16} and R_{17}, which may be identical or different, are selected from hydrogen and $(C_1\text{-}C_6)$alkyl,
  - X_6 represents a single bond, $-CH_2-$, an oxygen atom or a sulphur atom which is unsubstituted or substituted with one or two oxygen atom,
  - R_{20} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from $(C_1\text{-}C_6)$alkyl, halogen, hydroxyl, and amino, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur.

The invention also relates to the compounds of general formula (I) in which:

R_1 represents a group selected from hydrogen, mono$(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, di$(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$alkenyl, $(C_3\text{-}C_6)$alkynyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, and 3- to 6-membered cycloalkyl$(C_1\text{-}C_6)$alkyl,

W represents an oxygen atom, or a sulphur atom,

X_1 represents a nitrogen atom or a –CH group,

X_2 and X_3 represent a-CH group,

Y represents a group selected from oxygen atom, sulphur atom, -NH, and -N(C_1-C_6)alkyl,

Z represents an oxygen atom or a -NH group,

n is an integer from 1 to 3 inclusive,

Z_1 represents $-CR_8R_9$ wherein R_8 and R_9, independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl and hydroxy, and

- when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one double bond,
- or one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a –NH group,

A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,

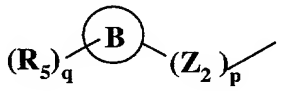
m is an integer from 0 to 3 inclusive,

the group(s) R_2, which may be identical or different, is (are) selected from (C_1-C_6)alkyl, halogen, -CN, $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, $-SO_2R_{10}$, $-(CH_2)_kSO_2NR_{10}R_{11}$, $-X_5(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$, $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$, $-(CH_2)_kC(=O)NR_{10}R_{11}$, and $-X_4-R_{12}$ in which:

- X_5 represents O, S or NH,
- k is an integer from 0 to 3 inclusive,
- R_{10} and R_{11}, which may be identical or different, are selected from hydrogen and (C_1-C_6)alkyl,
- X_4 represents $-CH_2-$, or an oxygen atom,

- R_{12} represents phenyl which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from $(C_1\text{-}C_6)$alkyl, halogen, and hydroxyl,

R_3 represents a group selected from methyl and the group of formula :



- ✓ in which p is an integer from 0 to 3 inclusive,
- ✓ Z_2 represents $-CR_{13}R_{14}$ wherein R_{13} and R_{14}, independently of each other, represent a group selected from hydrogen, $(C_1\text{-}C_6)$alkyl, and hydroxy, and
  - when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one double bond,
  - or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a $(C_1\text{-}C_6)$alkyl,
- ✓ B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,
- ✓ q is an integer from 0 to 3 inclusive,
- ✓ the group(s) R_5, which may be identical or different, is (are) selected from $(C_1\text{-}C_6)$alkyl, halogen, CN, NO_2, CF_3, OCF_3, $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2\text{-}N(R_{15})\text{-}(CH_2)_{k2}\text{-}NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O\text{-}(CH_2)_{k2}\text{-}NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, $-(CH_2)_kC(=O)NR_{15}R_{16}$, and $-X_6\text{-}R_{20}$ in which :
  - X_7 is S, O or NH,
  - k is an integer from 0 to 3 inclusive,
  - k1 is an integer from 0 to 2 inclusive,
  - k2 is an integer from 1 to 4 inclusive,

- R_{15}, R_{16} and R_{17}, which may be identical or different, are selected from hydrogen and $(C_1$-$C_6)$alkyl,
- X_6 represents a single bond, $-CH_2-$, an oxygen atom or a sulphur atom which is unsubstituted or substituted with one or two oxygen atom,
- R_{20} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from $(C_1$-$C_6)$alkyl, halogen, hydroxyl, and amino, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur.

The invention also relates to the compounds of general formula (I) in which:
R_1 represents hydrogen, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$alkenyl, aryl$(C_1$-$C_6)$alkyl, 3- to 6-membered cycloalkyl$(C_1$-$C_6)$alkyl,

W represents an oxygen atom,

X^1 represents -CH group or nitrogen atom ,and X^2 and X^3 represent each -CH group;

Y represents an oxygen atom,

Z represents an oxygen atom or a -NH group,

n is an integer from 1 to 3 inclusive,

Z_1 represents $-CR_8R_9$ wherein R_8 and R_9, independently of each other, represent a group selected from hydrogen and methyl, and

- when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one double bond,
- or one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a –NH group,

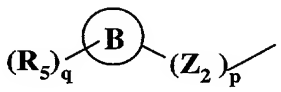
A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, and 1,3-benzodioxolyl,

m is an integer from 0 to 3 inclusive,

the group(s) R_2, which may be identical or different, is (are) selected from $(C_1\text{-}C_6)$alkyl, halogen, -CN, $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, $-SO_2R_{10}$, $-(CH_2)_kSO_2NR_{10}R_{11}$, $-X_5(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$, $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$, and $-(CH_2)_kC(=O)NR_{10}R_{11}$, in which:

- X_5 represents O, S or NH,
- k is an integer from 0 to 3 inclusive,
- R_{10} and R_{11}, which may be identical or different, are selected from hydrogen and $(C_1\text{-}C_6)$alkyl,

R_3 represents the group of formula :



- ✓ in which p is an integer from 0 to 3 inclusive,
- ✓ Z_2 represents $-CR_{13}R_{14}$ wherein R_{13} and R_{14}, independently of each other, represent a group selected from hydrogen, and methyl, and
  - when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one double bond,
  - or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a $(C_1\text{-}C_6)$alkyl,
- ✓ B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, and 1,3-benzodioxolyl,
- ✓ q is an integer from 0 to 3 inclusive,

- ✓ the group(s) R_5, which may be identical or different, is (are) selected from $(C_1\text{-}C_6)$alkyl, halogen, CN, NO_2, CF_3, OCF_3, $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2\text{-}N(R_{15})\text{-}(CH_2)_{k2}\text{-}NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O\text{-}(CH_2)_{k2}\text{-}NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, and $-(CH_2)_kC(=O)NR_{15}R_{16}$, in which :
  - X_7 is S, O or NH,
  - k is an integer from 0 to 3 inclusive,
  - k1 is an integer from 0 to 2 inclusive,
  - k2 is an integer from 1 to 4 inclusive,
  - R_{15}, R_{16} and R_{17}, which may be identical or different, are selected from hydrogen and $(C_1\text{-}C_6)$alkyl.

The invention also relates to the compounds of general formula (I) in which R_1 represents a hydrogen atom or a $(C_1\text{-}C_6)$alkyl group.

The invention also relates to the compounds of general formula (I) in which W represents an oxygen atom, Y represents an oxygen atom, Z represents a NH group, Z_1 represents a methylene group, and n is equal to one.

The invention also relates to the compounds of general formula (I) in which X_1 represents a -CH group or a nitrogen atom, and X_2 and X_3 represent each a-CH group.

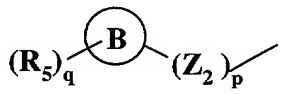
The invention also relates to the compounds of general formula (I) in which X_1 and X_3 represent each a –CH group, and X_2 represents a –CH group or a nitrogen atom.

The invention also relates to the compounds of general formula (I) in which X_1 and X_3 represent each a -CH group, and X_2 represents a nitrogen atom.

The invention also relates to the compounds of general formula (I) in which A represents a group selected from phenyl, pyridyl, 1,3-benzodioxolyl and benzofurazanyl, m is equal to

0 or 1, and R_2 represents a group selected from (C_1-C_6)alkoxy, hydroxy, halogen, and (C_1-C_6)thioalkoxy.

The invention also relates to the compounds of general formula (I) in which R_3 represents a group of formula :



in which:

p is equal to one,

Z_2 represents a methylen group,

B represents a group selected from phenyl, pyridyl, 1,3-benzodioxolyl, and benzofurazanyl,

q is an integer from 0 and 2 inclusive,

and R_5 represents a group selected from halogen, CN, $-(CH_2)_kNR_{15}R_{16}$, $-S(O)_{k1}R_{15}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-(CH_2)_kC(=O)OR_{15}$, $-X_6-R_{20}$ and $-(CH_2)_kC(=O)NR_{15}R_{16}$, in which :

k is an integer from 0 to 1 inclusive,

k1 is an integer from 0 to 2 inclusive,

R_{15} and R_{16}, which may be identical or different, are selected from hydrogen and (C_1-C_6)alkyl,

X_6 represents a single bond,

R_{20} represents a 5-menbered heterocyclic ring comprising from 3 to 4 heteroatoms selected from oxygen and nitrogen and optionally substituted by a methyl group or an oxo group.

Among the groups defined above, the following substituents are particularly preferred:

- halogen: F, Cl, Br, I, preferably F, Br and Cl;
- (C_1-C_6)alkyl: linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms;
- (C_1-C_6)alkoxy: linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms;

- (C_3-C_6)alkenyl: containing from 3 to 6 and preferably 3 or 4 carbon atoms, more particularly allyl;
- (C_3-C_6)alkynyl: containing from 3 to 6 and preferably 3 or 4 carbon atoms, more particularly propargyl;
- aryl: containing from 5 to 10 and preferably 5 or 6 carbon atoms;
- heteroaryl: aryl group interrupted with one or several hetero atom selected from nitrogen, oxygen and sulphur. The term "interrupted" means that the hetero atom can replace a carbon atom of the ring. Examples of such groups containing a heteroatom are, inter alia, thienyl, pyridyl, benzofurazanyl;
- heterocycle: an aromatic or non-aromatic, 5-or 6-membered monocycle comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur.
- aryl(C_1-C_6)alkyl in which the alkyl contains from 1 to 6 and preferably from 1 to 4 carbon atoms;
- cycloalkyl: containing from 3 to 8 and preferably from 3 to 6 carbon atoms,
- cycloalkyl(C_1-C_6)alkyl in which the alkyl contains from 1 to 6 and preferably from 1 to 3 carbon atoms and the cycloalkyl contains from 3 to 6 carbon atoms.
- multiple bond represent a double bond or a triple bond.

Among the compounds of the present invention that are preferred are the compounds described below in Examples 1 to Example 227.

More particularly, the preferred compounds of the present invention are compound of formula (I) which are:

- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide
- 4-[6-(4-Fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- 1-Methyl-2,4-dioxo-3-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid hemicalcium salt
- Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoate
- 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H* - quinazolin-3-ylmethyl]-benzoic acid
- 1-Methyl-2,4-dioxo-3-[4-(2H-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- Methyl 2-hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide
- 4-{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid
- 2-Hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide
- 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- Methyl 4-{6-[(1,3-benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate
- 1-Methyl-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 1-Methyl-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide
- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H]-quinazolin-3-ylmethyl]-benzoic acid

- 1-{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid
- 4-Pyridylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylate
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Dimethylcarbamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 1-Methyl-3-[4-(2-methyl-2*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide
- Benzo[1,3]dioxol-5-ylmethyl-3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide
- 1-Methyl-3-(4-methylcarbamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 4-[6-(4-Hydroxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- Methyl 4-[6-(4-fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
- 3-(4-Chlorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide
- 1-Methyl-3-[4-(1-methyl-1*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

- 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide
- 4-Pyridylmethyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
- 1-Methyl-2,4-dioxo-3-pyridin-4-ylmethyl-1,2,3,4-tetrahydro-quinazoline-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Amino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 1-Methyl-3-(4-nitro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 1-Methyl-2,4-dioxo-3-(4-sulfamoyl-benzyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
- 2-Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid
- 3-(3-fluoro-4-methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy benzylamine

- 4-[1-Ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide
- 3-(2'-Cyano-biphenyl-4-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 4-[1-Methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- 4-{6-[(Benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid
- Methyl 2-methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
- 3-(4-Acetylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(Benzo[1,3]dioxol-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide
- 3-(4-Dimethylcarbamoylmethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-acetic acid
- (4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-phenyl)-acetic acid
- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide
- Methyl {4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-acetate
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
- 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

- 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- Methyl 4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate
- 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
- 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
- 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid
- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid hemimagnesium salt
- Example 164: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid
- 3-[4-(N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- Ethyl 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
- 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- and 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide.

The invention also relates to the pharmaceutically acceptable salts of the compounds of formula (I). A review of the pharmaceutically acceptable salts will be found in J. Pharm. Sci., 1977, vol. 66:1-19. However, the expression "pharmacologically acceptable salts of a compound of formula (I) with a basic function" means the addition salts of the compounds of formula (I) formed from non-toxic mineral or organic acids such as, for example, hydrobromic acid, hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, acetic acid, succinic acid, tartaric acid, citric acid, maleic acid, hydroxymaleic acid, benzoic acid, fumaric acid, toluenesulphonic acid, isethionic acid and the like. The various quaternary ammonium salts of the compounds of formula (I) are also included in this category of

compounds of the invention. In addition, the expression “pharmacologically acceptable salts of a compound of formula (I) with an acid function” means the usual salts of the compounds of formula (I) formed from non-toxic mineral or organic bases such as, for example, the hydroxides of alkali metals and of alkaline-earth metals (sodium, potassium, magnesium and calcium), amines (dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like) or quaternary ammonium hydroxides such as tetramethylammonium hydroxide.

As mentioned above, the compounds of formula (I) of the present invention are matrix metalloprotease inhibitors, and more particularly inhibitors of the enzyme MMP-13.

In this respect, their use is recommended in the treatment of diseases or complaints involving a therapy by MMP-13 inhibition. By way of example, the use of the compounds of the present invention may be recommended during the treatment of any pathology in which a destruction of extracellular matrix tissue is involved, and most particularly pathologies such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and certain cancers.

<u>Selectivity of the compounds of formula (I) for the enzyme MMP-13</u>

Most of the matrix metalloprotease inhibitors described in the prior art are non-selective inhibitors, capable of simultaneously inhibiting several matrix metalloproteases. For example, compounds such as CGS-27.023A and AG-3340 (Montana and Baxter (2000)) inhibit both MMP-1, MMP-2, MMP-3, MMP-9 and MMP-13, i.e. these compounds of the prior art inhibit MMPs of both collagenase, gelatinase and stromelysin type.

It has been shown according to the invention that compounds of general formula (I) are selective inhibitors of MMP-13. “Selective inhibitors of MMP-13” refers to a compound of formula (I) which have an IC_{50} for MMP-13 at least 5 time lower than the IC_{50} for a MMP distinct from MMP-13, and preferably at least 10 times, 15 times, 20 times, 30 times, 40 times, 50 times, 100 times or 1000 times lower than the IC_{50} value for a MMP distinct from MMP-13.

A MMP distinct from MMP-13 refers preferably to a matrix metalloprotease selected from MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14.

In particular, it has been shown according to the invention that the compounds of general formula (I), and more particularly the family of compounds given as examples in the present description, have an IC_{50} value for the enzyme MMP-13 which is often 1 000 times lower than the value of their IC_{50} for other matrix metalloproteases, in particular MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14.

The result of this is that the compounds of general formula (I) according to the invention are particularly useful in the treatment of complaints mainly associated with a physiological imbalance between the MMP-13 enzymes and their natural tissue inhibitors.

PHARMACEUTICAL FORMULATION OF THE COMPOUNDS OF THE INVENTION

A subject of the present invention is also a pharmaceutical composition comprising a compound of general formula (I) as defined above and a pharmaceutically acceptable excipient.

The invention also relates to the use of a compound of general formula (I) as defined above for the preparation of a medicinal product intended for treating a disease or complaint involving therapy by inhibition of matrix metalloprotease, and more particularly a disease or complaint involving therapy by inhibition of type-13 matrix metalloprotease (MMP-13) such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and cancers.

The invention also relates to a method for treating a pathology associated with an imbalance in the activity of MMPs, and more specifically of MMP-13, the said method comprising a step during which a pharmaceutically effective amount of an MMP-inhibitor compound according to the invention, or a pharmaceutical composition containing this compound, is administered to a patient requiring such a treatment.

Among the various pathologies associated with an imbalance in MMP activity, an MMP-13-inhibitor compound of general formula (I) according to the invention is particularly useful for treating all pathologies brought about by a degradation of extracellular matrix tissue, and more particularly for treating rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and cancer.
In an entirely preferred manner, a compound of general formula (I) as defined according to the invention will be used, preferably to treat arthritis, osteoarthritis and rheumatoid arthritis.

The compounds of the invention are administered in the form of compositions that are suitable for the nature and gravity of the complaint to be treated. The daily dosage in man is usually between 2 mg and 1 g of product which may be absorbed in one or more dosage intakes. The compositions are prepared by methods that are common to those skilled in the art and generally comprise 0.5% to 60% by weight of active principle (compound of formula I) and 40% to 99.5% by weight of pharmaceutically acceptable vehicle.

The compositions of the present invention are thus prepared in forms that are compatible with the desired route of administration. By way of example, the following pharmaceutical forms may be envisaged, although the list given below is not limiting:

1) Forms for oral administration:

Drinkable solutions, suspensions, sachets of powder for drinkable solution, sachets of powder for drinkable suspension, gastro-resistant gel capsules, sustained-release forms, emulsions, HPMR capsules or gel capsules, lyophilizates to be melted under the tongue.

2) Forms for parenteral administration:

Intravenous route:

Aqueous solutions, water/cosolvent solutions, solutions using one or more solubilizing agents, colloidal suspensions, emulsions, nanoparticulate suspensions which can be used for the injection of sustained-release forms, dispersed forms and liposomes.

Subcutaneous/intramuscular route:

In addition to the forms which can be used intravenously and which can also be used for the subcutaneous and intramuscular routes, other types of forms such as suspensions, dispersed forms, sustained-release gels and sustained-release implants may also be used.

3) Forms for topical administration:

Among the most common topical forms that are distinguished are creams, gels (aqueous phases gelled with polymers), patches, which are dressings to be stuck directly onto the skin and which can be used to treat dermatosis without percutaneous penetration of the active substance, sprays, emulsions and solutions.

4) Forms for pulmonary administration

Forms such as solutions for aerosols, powders for inhalers and other suitable forms are distinguished in this category.

5) Forms for nasal administration:

This especially relates herein to solutions for drops.

6) Forms for rectal administration:

Suppositories and gels will be selected, inter alia.

It is also possible to envisage using forms allowing the administration of ophthalmic solutions or allowing the vaginal administration of the active principle.

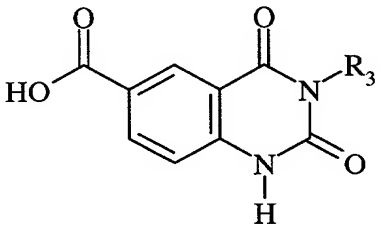
Another important category of pharmaceutical form which may be used in the context of the present invention relates to forms for improving the solubility of the active principle. By way of example, it may be envisaged to use aqueous solutions of cyclodextrin, and more particularly forms comprising hydroxypropyl-β-cyclodextrin. A detailed review of this type of pharmaceutical form is presented in the article published under the reference

Journal of Pharmaceutical Sciences, 85 (11), 1142-1169 (1996), and incorporated into the present patent application by reference.

The various pharmaceutical forms recommended above are described in detail in the book "Pharmacie galénique" by A. Lehir (published by Masson, 1992 (6th edition)), which is incorporated into the present patent application by reference.

INTERMEDIATE COMPOUNDS

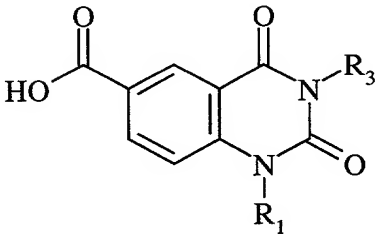
The present invention also relates to an intermediate compound of general formula (III)



(III)

in which R^3 has the same meaning as for the compound of general formula (I).

According to another aspect, the present invention also relates to an intermediate compound of general formula (IV):



(IV)

in which R_1 and R_3 have the same meaning as that defined above for the compound of general formula (I).

PROCESSES FOR SYNTHESIZING THE COMPOUNDS OF GENERAL FORMULA (I)

Throughout this application the following abbreviations have the meanings listed below:

DEAD: Diethyl azodicarboxylate

DIPEA: *N,N*-diisopropylethylamine

DMF: *N,N*-dimethylformamide

NMP: 1-methyl-2-pyrrolidinone

THF: tetrahydrofuran

TOTU: O-[(ethoxycarbonyl)cyanomethylenamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate

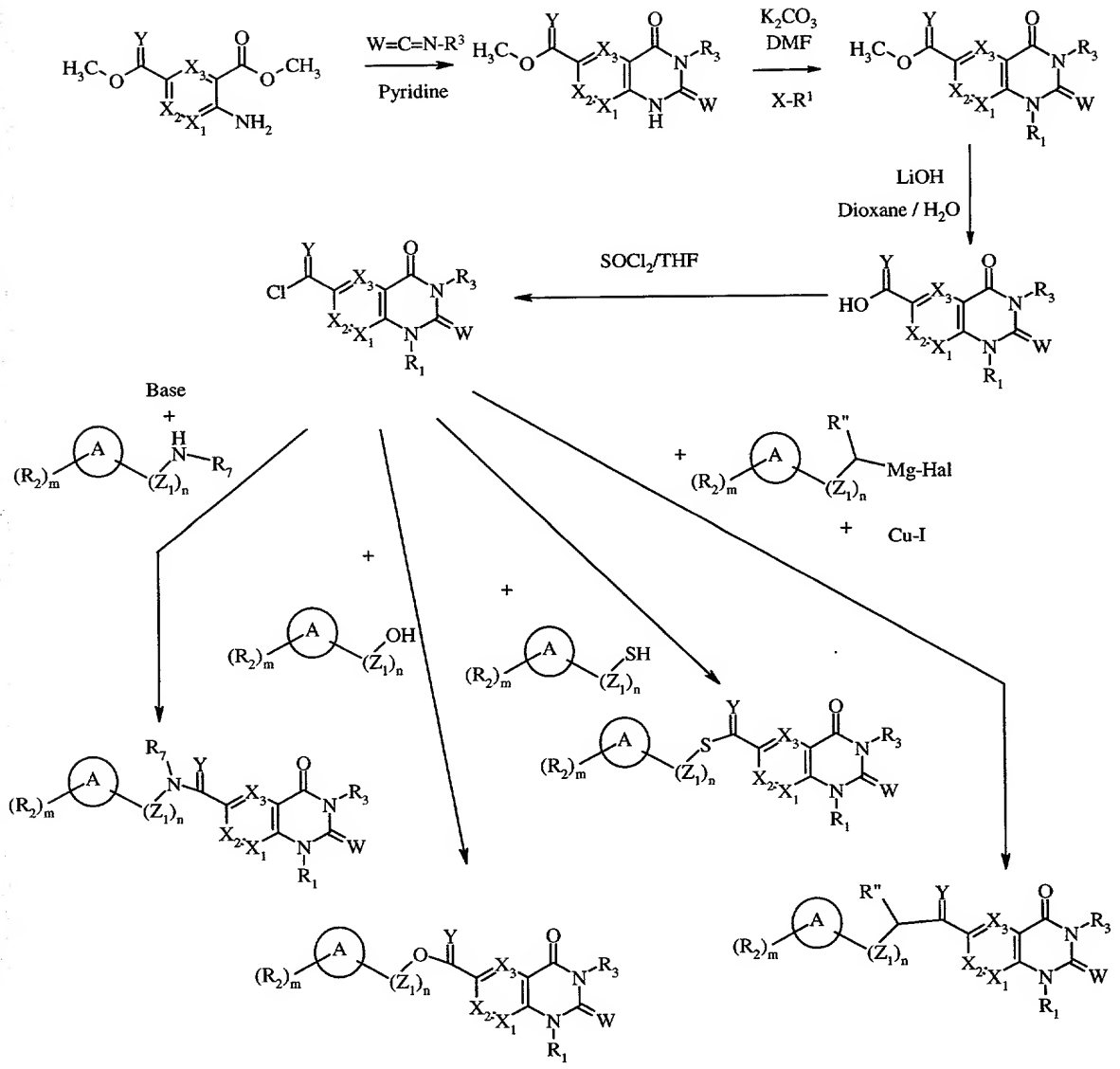
EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

HOBT: 1-hydroxybenzotriazole hydrate

The compounds according to the present invention can be obtained by carrying out several synthetic processes. Some of these synthetic processes are described below:

A) General process:

A general process for the synthesis of the compounds of general formula (I) is described in the following scheme:

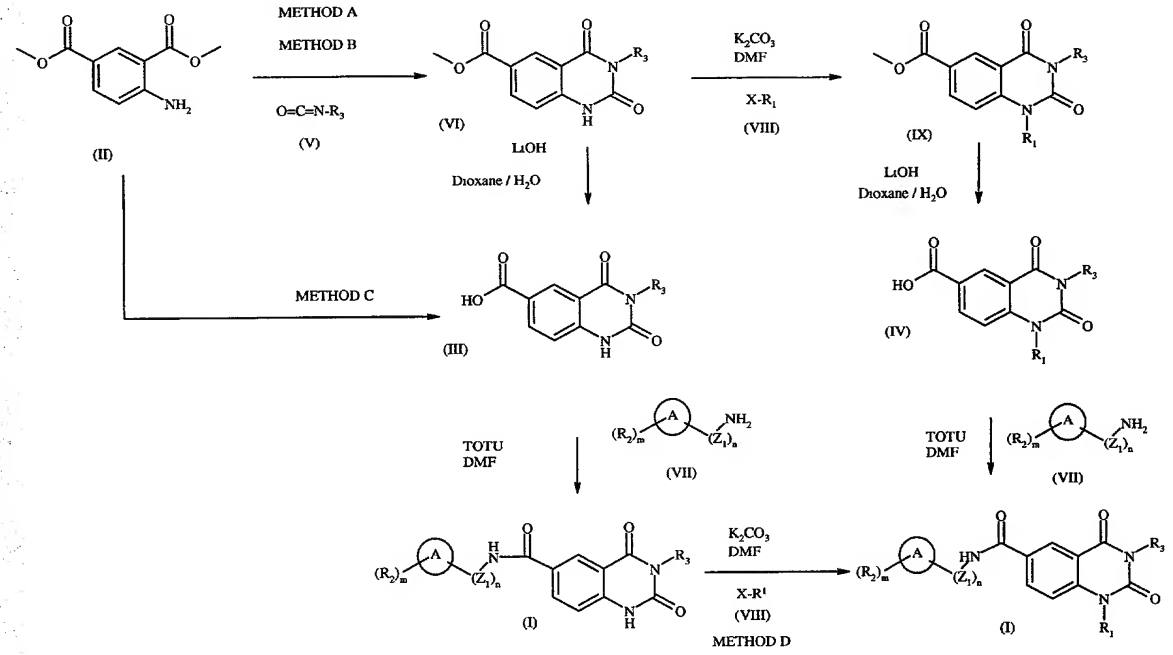


in which R_7 is hydrogen, (C_1-C_6)alkyl, aryl(C_1-C_6)alkyl, cycloalkyl, aryl or heteroaryl, R'' is (C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, aromatic or non-aromatic heterocycle or cycloalkyl, and R_1, R_2, R_3, X_1, X_2, X_3, A, W, Y, Z_1, n and m have the same meaning as that defined above for the compound of formula (I).

B) Synthetic process No. 1

The compounds of the present invention may be obtained firstly by the method represented in Scheme 1 below.

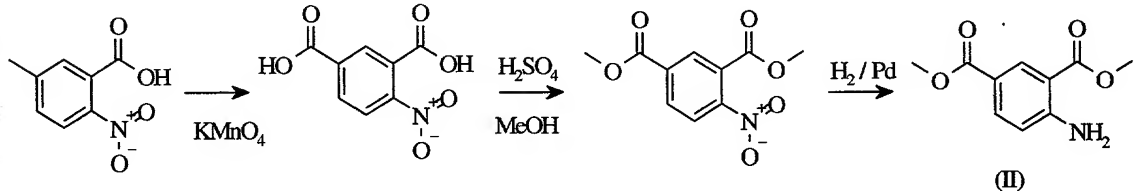
Scheme 1



in which each of the generic substituents is as defined for the compound of general formula (I).

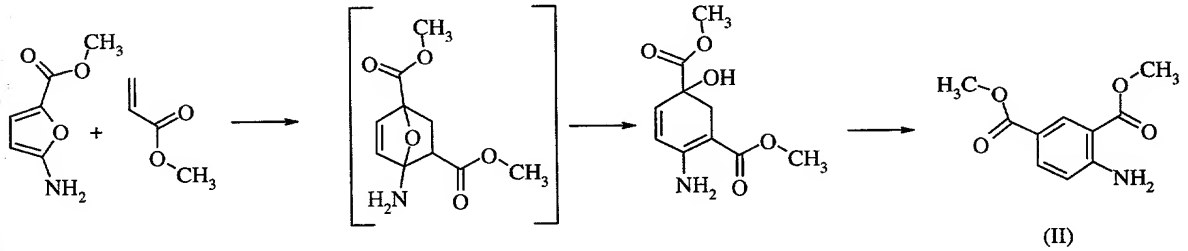
The intermediate compound of formula (II) which constitutes the starting material for the synthetic process illustrated by Scheme 1 above may be prepared in accordance with Scheme 2 below:

Scheme 2



The intermediate compound of formula (II) which constitutes the starting material in the process to synthesize the compounds of general formula (I) according to the invention as illustrated in Scheme 1 above may also be prepared according to the process illustrated in Scheme 3 below.

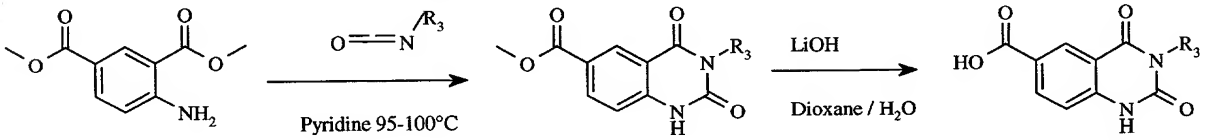
Scheme 3



(II)

The compound of general formula (III) may be prepared, in accordance with the process described in Scheme 1 above, from the compound of formula (II), according to the synthetic Scheme 4 (Method A) below:

Scheme 4 / Method A

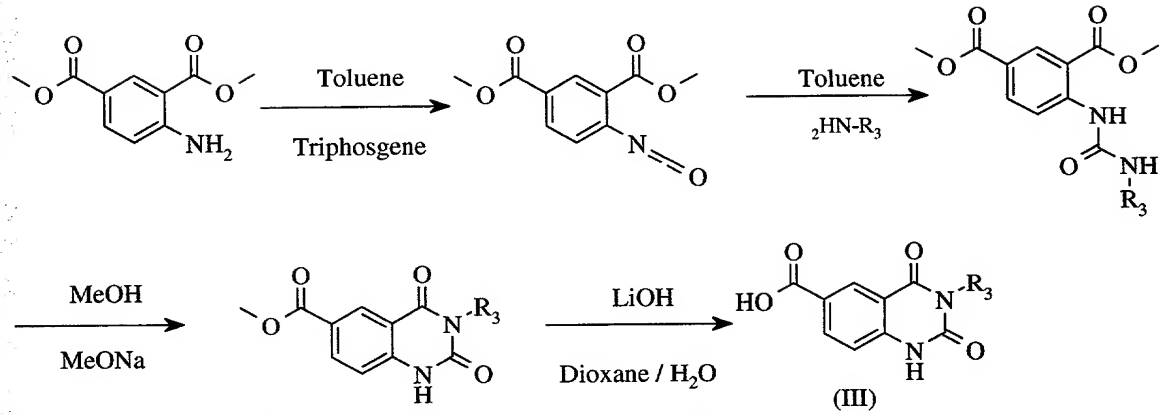


(III)

in which R_3 is as defined above for the compound of general formula (I).

According to another aspect, the intermediate compound of formula (III) may be prepared, in accordance with the synthetic process illustrated in Scheme 1 above, according to Method B, as illustrated in Synthetic Scheme 5 below:

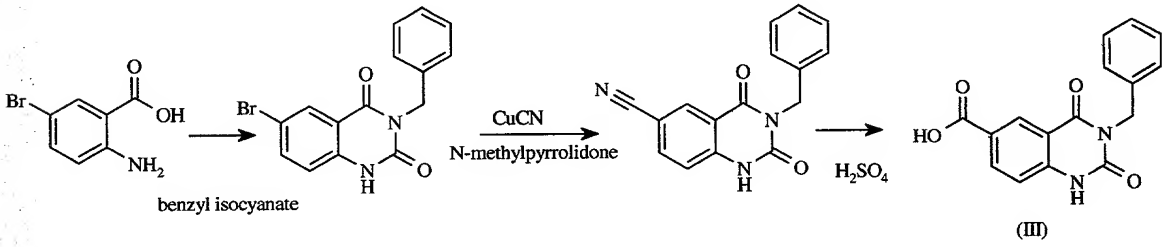
Scheme 5 / Method B



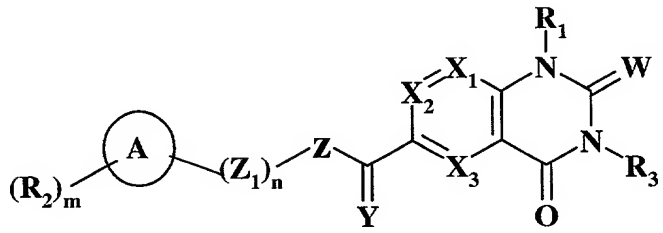
in which R_3 is as defined for the compound of general formula (I).

According to yet another aspect, an intermediate compound of general formula (III), in which R_3 is a benzyl radical, may be obtained, in accordance with the synthetic process illustrated in Scheme 1 above, according to Method C illustrated in Synthetic Scheme 6 below:

Scheme 6 / Method C



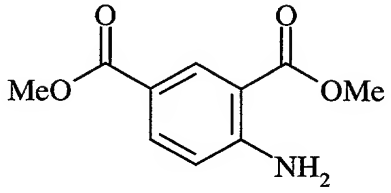
Consequently, a subject of the invention is also a process for manufacturing a compound of general formula (I):



(I)

in which R_1, R_2, R_3, Z_1, A, n and m are as defined in the summary of the invention, X_1, X_2 and X_3 are CH, Y is O, Z is N-R_7 and W is O,

the said process being characterized in that it comprises the reaction of a compound of formula (II):

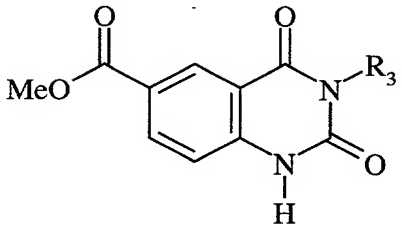


(II)

with pyridine and the compound of general formula (V):

$$O=C=N-R_3, \qquad (V)$$

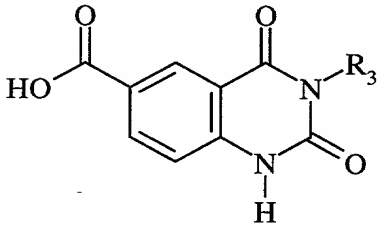
in which R_3 is as defined in the summary of the invention, to give the compound of general formula (VI):



(VI)

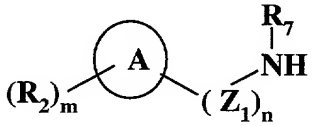
in which R_3 is as defined hereinbefore,

followed by reacting the compound of general formula (VI) in the presence of LiOH to give the compound of general formula (III) in which R_3 is as defined in the summary of the invention.



(III)

The above process is also characterized in that the compound of general formula (III) in which R_3 is as defined for the compound of general formula (I), is reacted, in the presence of an acid activator such as TOTU, with the compound of general formula (VII):



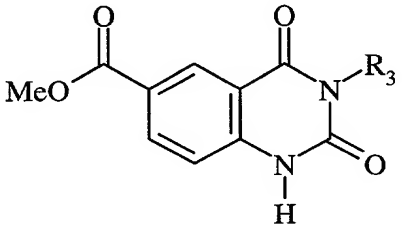
(VII)

in which R_7 is selected from hydrogen, $(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2, Z_1, m and n are as defined for the compound of general formula (I),

to give the compound of general formula (I) in which R_1 represents H, X_1, X_2 and X_3 are CH, Y is O, Z is N-R_7, W is O, and A, R_2, R_3, Z_1, m and n are as defined hereinbefore.

The present invention also relates to a process for manufacturing a compound of general formula (I) in which R_1, R_2, R_3, A, Z_1, m and n are as defined for the compound of general formula (I), X_1, X_2 and X_3 are CH, W is O, Y is O and Z is N-R_7,

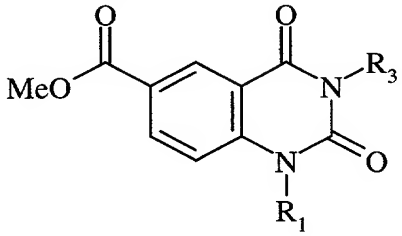
the said process being characterized in that a compound of general formula (VI):



(VI)

in which R_3 is as defined in the summary of the invention,

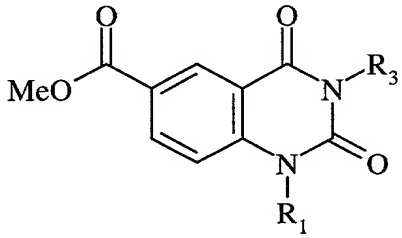
is reacted, in the presence of a base, with compound (VIII) of general formula X-R_1, in which R_1 is as defined in the summary of the invention and X is a leaving group such as halogen, to give the compound of general formula (IX):



(IX)

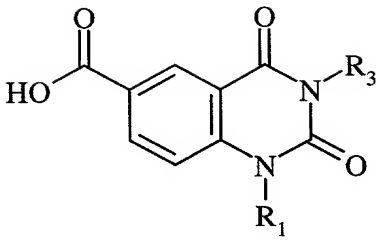
in which R_1 and R_3 are as defined hereinbefore.

The above process is also characterized in that the compound of general formula (IX):



(IX)

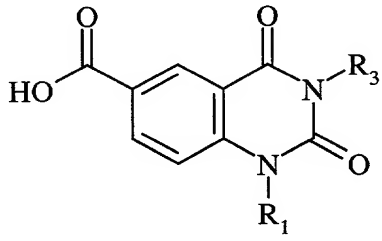
is reacted in the presence of LiOH to give the compound of general formula (IV):



(IV)

in which R_1 and R_3 are as defined hereinbefore.

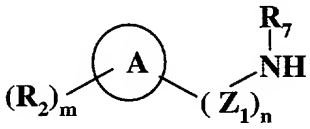
The above process is also characterized in that the compound of general formula (IV):



(IV)

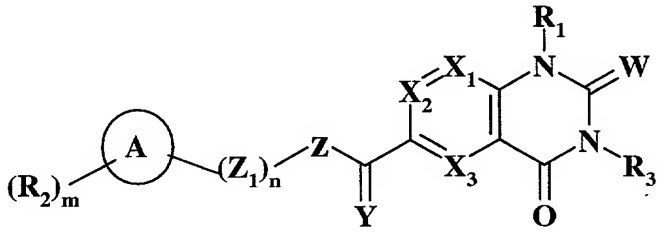
in which R_3 is as defined in the compound of general formula (I),

is reacted, in the presence of an acid activator such as TOTU, with the compound of general formula (VII)



(VII)

in which R_7 is selected from hydrogen, $(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2, Z_1, m and n are as defined in the summary of the invention, to give the compound of general formula (I):

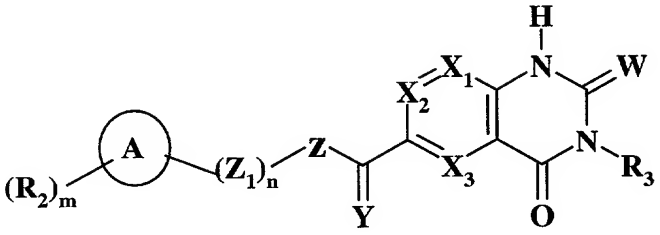


(I)

in which R_1, R_2, R_3, A, Z_1, m and n are as defined in the summary of the invention, X_1, X_2 and X_3 are CH, W is O, Y is O and Z is N-R_7.

Another subject of the present invention is a process for manufacturing the compound of general formula (I) in which R_1, R_2, R_3, W, X_1, X_2, X_3, A, Z_1, m and n are as defined for

the compound of general formula (I), Y is O and Z is N-R_7, characterized in that a compound of general formula (I) in which R_1 is H,

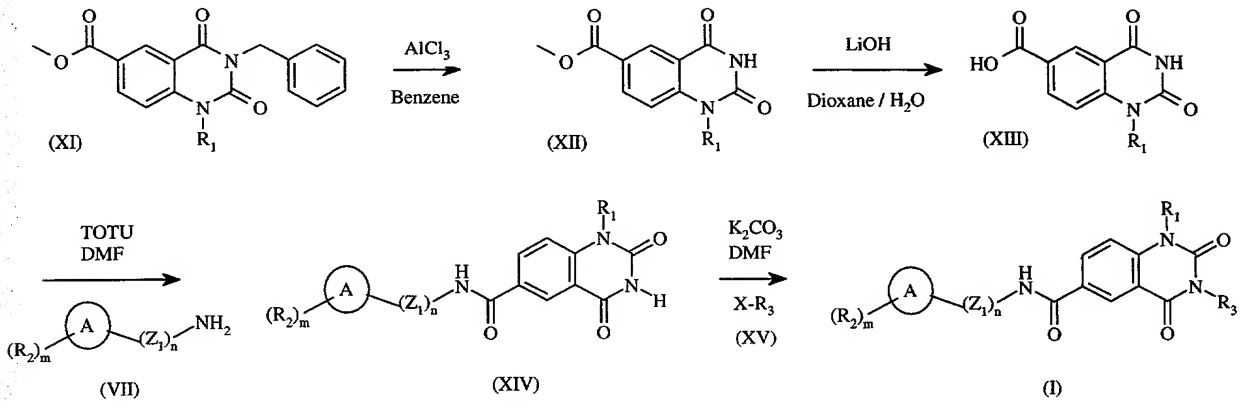


is reacted, in the presence of a base, with a compound (VIII) of general formula X-R_1, in which R_1 is as defined in the summary of the invention and X is a leaving group such as halogen, to give the compound of general formula (I) in which R_1 is as defined in the summary of the invention.

C. Synthetic process No. 2

The compounds of the present invention can also be obtained by the method represented in Scheme 7 below:

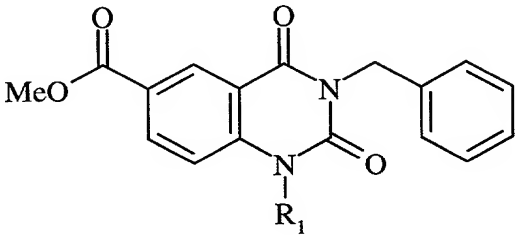
Scheme 7



in which each of the generic substituents is as defined for the compound of general formula (I).

The present invention also relates to a process for manufacturing a compound of general formula (I) in which X_1, X_2 and X_3 are CH, W is O, Y is O, Z is N-R_7, R_1, R_3, A, R_2, Z_1, m

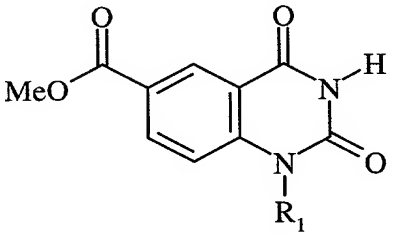
and n are as defined for the compound of general formula (I) characterized in that a compound of general formula (XI):



(XI)

in which R_1 is as defined hereinbefore,

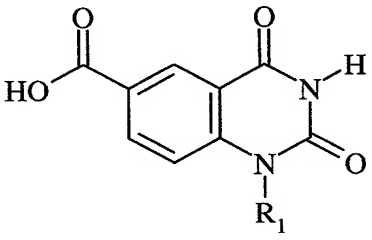
is reacted with $AlCl_3$ in a solvent such as benzene, to give the compound of general formula (XII):



(XII)

in which R_1 is as defined hereinbefore.

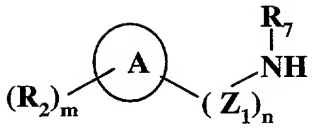
The process for manufacturing a compound of general formula (I) above is also characterized in that it comprises a step in which the compound of general formula (XII) is reacted in the presence of LiOH and a mixture of dioxane/H_2O to give the compound of general formula (XIII):



(XIII)

in which R_1 is as defined hereinbefore.

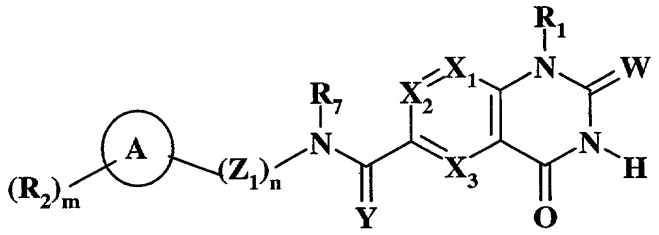
The process for manufacturing a compound of general formula (I) above is also characterized in that it comprises a step in which the compound of general formula (XIII) is reacted, in the presence of an acid activator such as TOTU with the compound of general formula (VII):



(VII)

in which R_7 is selected from hydrogen, $(C_1$-$C_6)$alkyl, aryl$(C_1$-$C_6)$alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2, Z_1, m and n are as defined in the summary of the invention,

to give the compound of general formula (XIV) in which X_1, X_2 and X_3 are CH, W is O, Y is O, and R_7, R_1, A, R_2, Z_1, m and n are as defined hereinbefore:



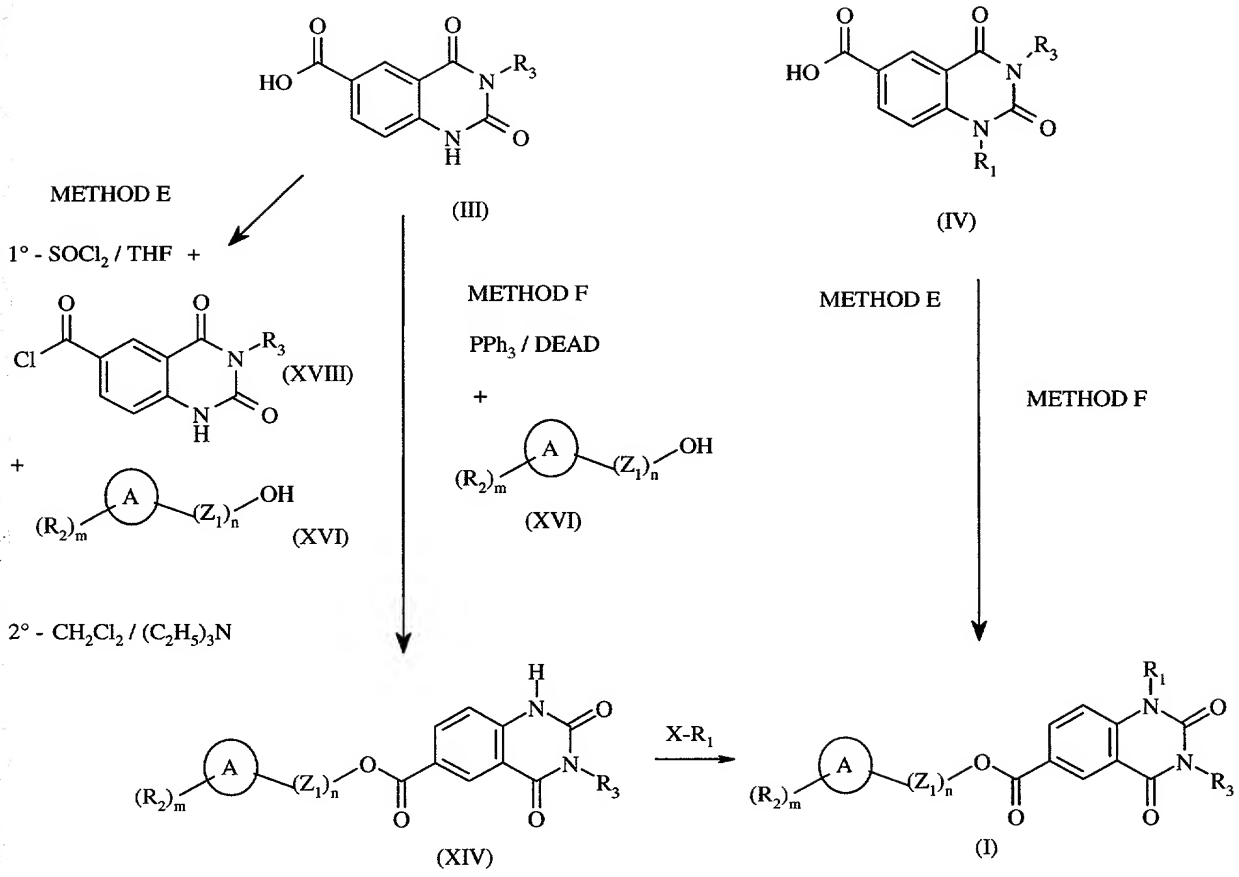
(XIV)

The process for manufacturing a compound of general formula (I) above is also characterized in that it comprises a step in which the compound of general formula (XIV) is reacted with compound (XV) of general formula X-R_3, in which R_3 is as defined in the summary of the invention and X is a leaving group such as halogen, to give the compound of general formula (I) in which X_1, X_2 and X_3 are CH, W is O, Y is O, Z is N-R_7, and R_7, R_1, A, R_2, Z_1, m and n are as in the compound of genral formula (I).

D. Preparation process No. 3

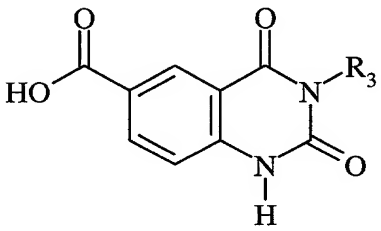
The compounds of general formula (I) of the present invention may also be obtained by the method represented in Scheme 8 below:

Scheme 8



In this scheme, each generic substituent is as defined for the compound of general formula (I) above.

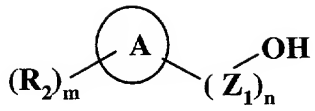
Thus, the present invention also relates to a process for manufacturing a compound of general formula (I) as defined above in which X_1, X_2 and X_3 are CH, W is O, Y is O and Z is O, characterized in that a compound of general formula (III):



(III)

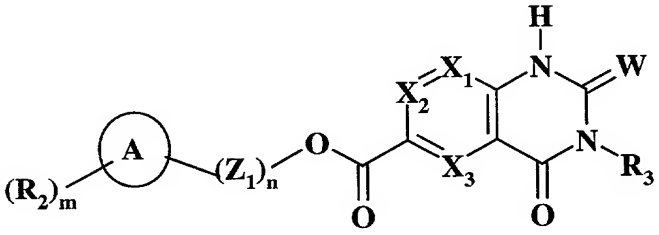
in which R_3 is as defined in the compound of general formula (I),

is reacted with a compound of general formula (XVI):



(XVI)

in which and A, R_2, Z_1, m and n are as defined in the compound of general formula (I), to give a compound of general formula (XVII):



(XVII)

in which A, R_2, R_3, Z_1, m and n are as defined in the summary of the invention, X_1, X_2 and X_3 are CH, and W is O.

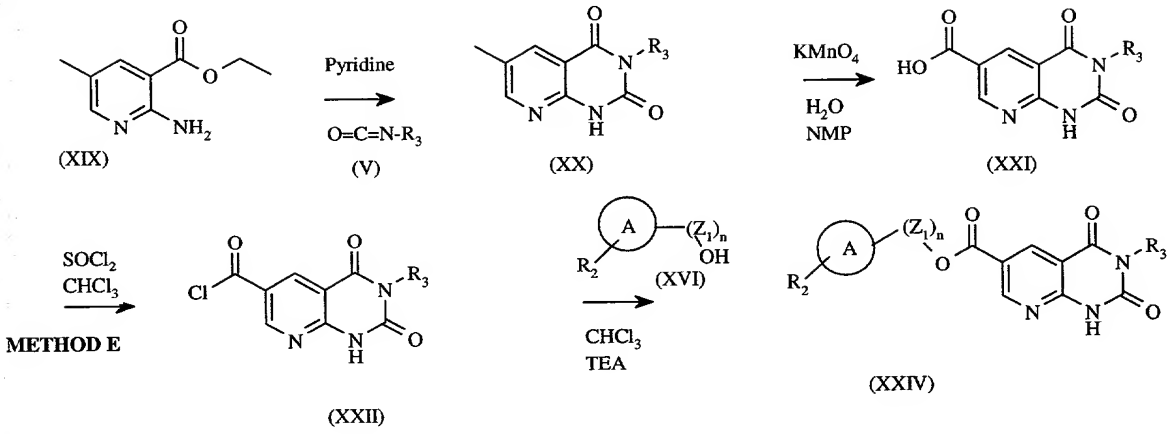
According to the process for manufacturing a compound of general formula (I) above, the said process also comprises a step in which the compound of formula (XVII) is reacted, in the presence of a base, with compound (VIII) of general formula X-R_1, in which R_1 is as defined in the summary of the invention and X is a leaving group such as halogen, to give the compound of general formula (I) in which X_1, X_2 and X_3 are CH, W is O, Y is O, Z is O, and A, R_2, R_3, R_1, Z_1, m and n are as defined in the summary of the invention

The present invention also relates to a process for manufacturing a compound of general formula (I) as defined above, characterized in that it comprises a step in which a compound of general formula (IV) is reacted with a compound of general formula (XVI) to give a compound of general formula (I) in which X_1, X_2 and X_3 are CH, W is O, Y is O and Z is O.

E. Preparation process No. 4

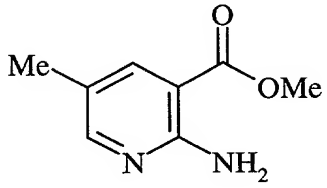
The compounds of the present invention, and most particularly the compounds of the invention which constitute pyridine esters, may be obtained by the method represented in Scheme 9 below:

Scheme 9



in which each of the generic substituents on the intermediate compounds has the same meaning as for the compound of general formula (I) as defined in the summary of the invention.

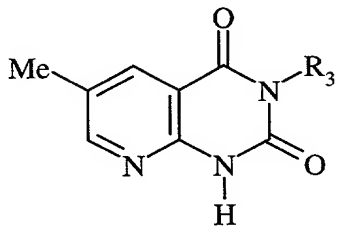
Consequently, a subject of the present invention is also a process for manufacturing a compound of general formula (I) in which X_2 and X_3 are CH, X_1 is N, Z is O and Y is O, characterized in that the said process comprises a step in which a compound of general formula (XIX):



(XIX)

is reacted with pyridine and a compound (V) of general formula O=C=N-R_3 in which R_3 is as defined in the compound of general formula (I),

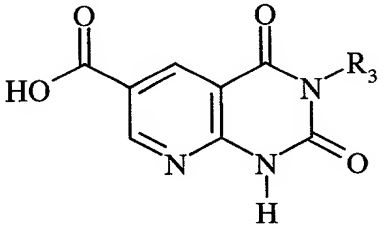
to give a compound of general formula (XX):



(XX)

in which R_3 is as defined hereinbefore.

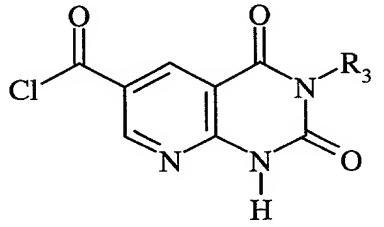
The process for manufacturing a compound of general formula (I) above is also characterized in that it comprises a step in which the compound of general formula (XX) is reacted in the presence of $KMnO_4$ to give the compound of general formula (XXI):



(XXI)

in which R_3 is as defined hereinbefore.

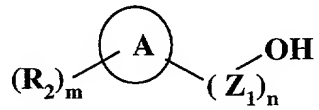
The above process is also characterized in that it comprises a step in which a compound of general formula (XXI) is reacted in the presence of $SOCl_2$ and $CHCl_3$ to give the compound of general formula (XXII):



(XXII)

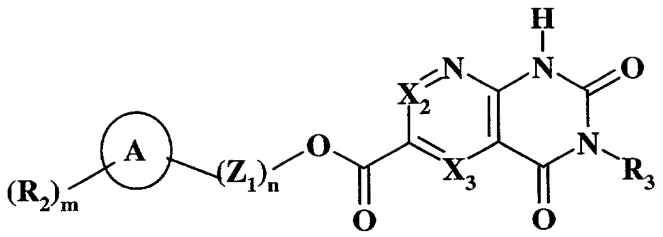
in which R_3 is as defined hereinbefore.

The process for manufacturing a compound of general formula (I) according to the invention is also characterized in that it comprises a step in which the compound of formula (XXII) is reacted with the compound of general formula (XVI):



(XVI)

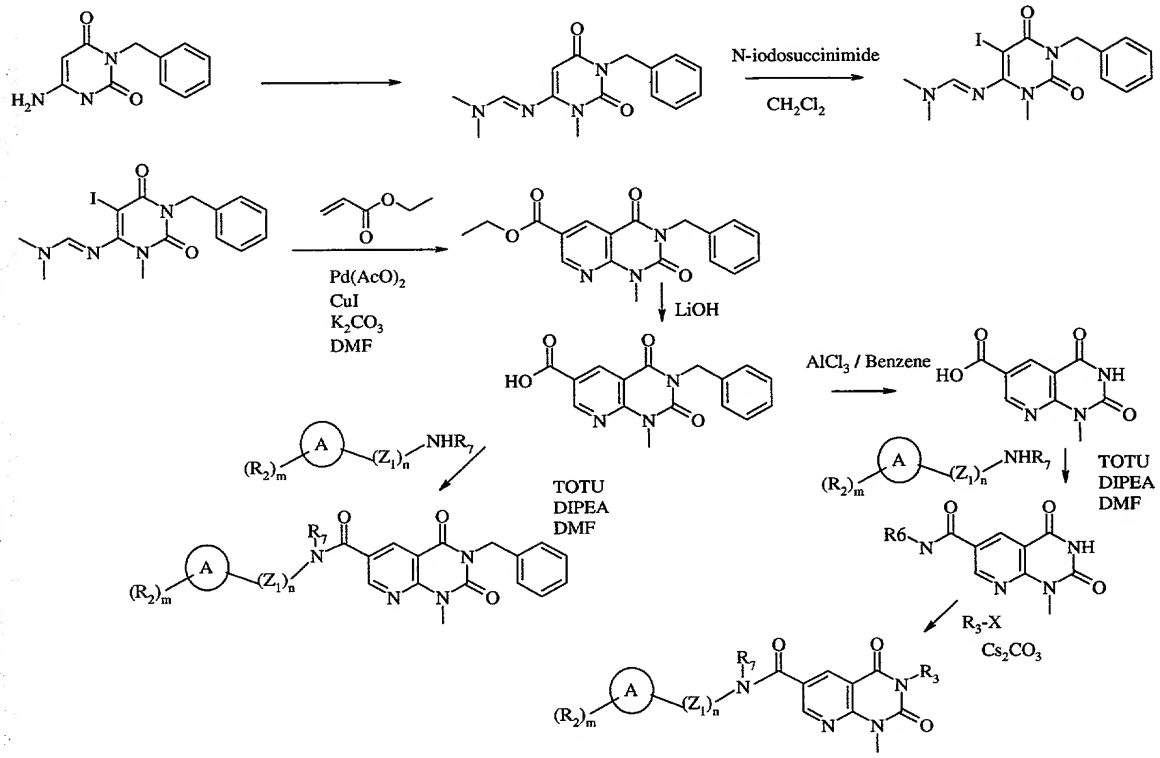
in which A, R_2, Z_1, m and n are as defined in the compound of general formula (I),
to give the compound of general formula (XXIV) in which X_2 and X_3 are CH and A, n, m, Z_1, R_2 and R_3 are as defined in the summary of the invention/



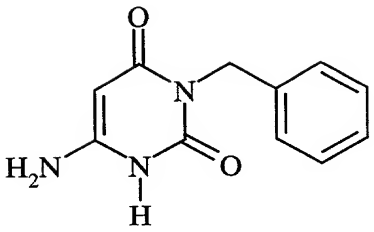
(XXIV)

The compounds of the present invention which constitute pyridine amide can also be obtained by the method represented in scheme 10 below:

Scheme 10

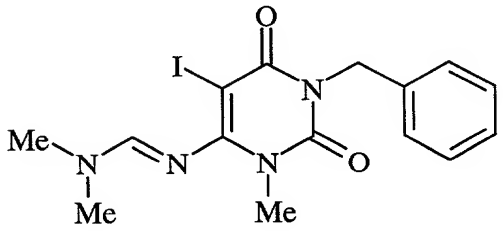


Consequently, a subject of the present invention is also a process for manufacturing a compound of genral formaula (I) in which X_2 and X_3 are CH, X_1 is N, Z is $-NR_7$ in which R_7 is as defined in the compound of formual (I), W is O, and Y is O, characterized in that the said process comprises a step in which a compound of general (XXV):



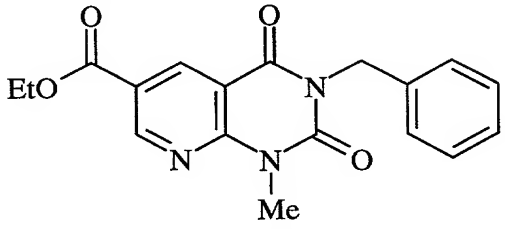
(XXV)

is reacted in a first step with N,N'-dimethylformamide dimethyl acetal under reflux of DMF , and in a second step with N-iodosuccinimide, to give a compound of formula (XXVI):



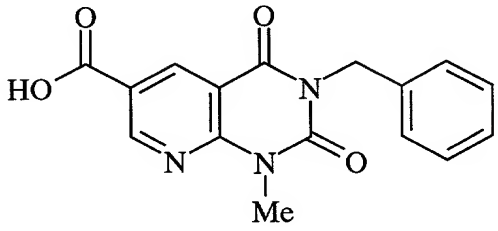
(XXVI)

followed by reacting th compound of formula (XXVI) whith ethyl acrylate in the presence of palladium diacetate, CuI and a base, to give the compound of general formula (XXVII):



(XXVII)

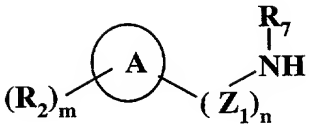
followed by reacting the compound of formula (XXVII) in the presence of LiOH to give the compound of general formula (XXVIII):



(XXVIII)

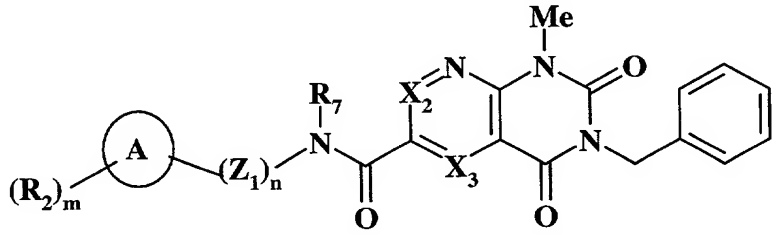
the said compound of formula (XXVIII) :

- either is reacted, in the presence of an acid activator such as TOTU, with the compound of formula (VII):



(VII)

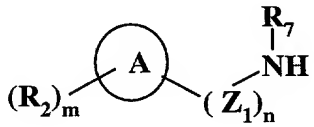
in which R_7 is selected from hydrogen, $(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2, Z_1, m and n are as defined in the summary of the invention,
to give the compound of general formula (XXIX):



(XXIX)

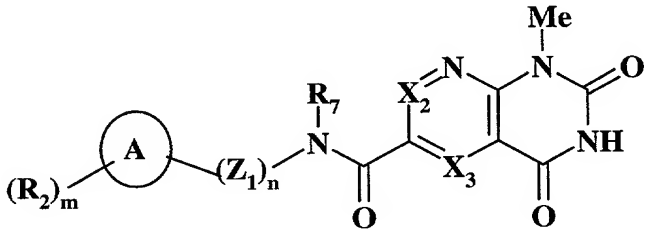
in which A, R_2, R_7, Z_1, m and n are as defined hereinbefore, and X_2 and X_3 represents each -CH group,

- or is reacted in a first step with $AlCl_3$ in the presence of benzene, and in a second step in the presence of an acid activator such as TOTU, with the compound of formula (VII):



(VII)

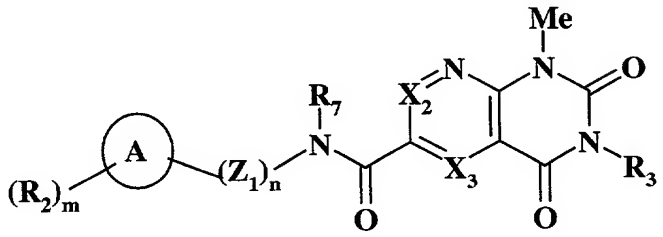
in which R_7 is selected from hydrogen, $(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2, Z_1, m and n are as defined in the summary of the invention,
to give the compound of general formula (XXX):



(XXX)

in which A, R_2, R_7, Z_1, m and n are as defined hereinbefore, and X_2 and X_3 represents each -CH group,

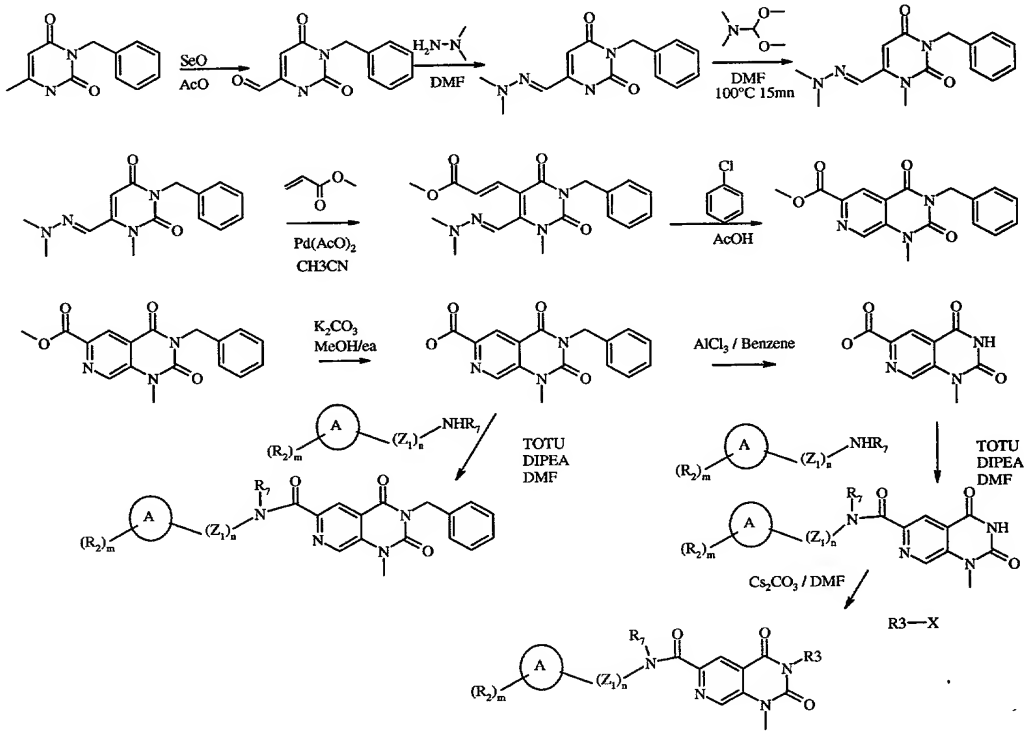
followed by reacting the compound of formula (XXX) with a compound of formula R_3-X in which R_3 is as defined in the compound of general formula (I), in the presence of a base, to give the compound of formula (XXXI):



(XXXI)

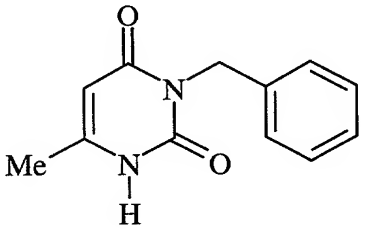
The compounds of the present invention which constitute pyridine amide, and particularly pyrido[3,4-d]pyrimidine derivatives, can also be obtained by the method represented in scheme 11 below:

Scheme 11



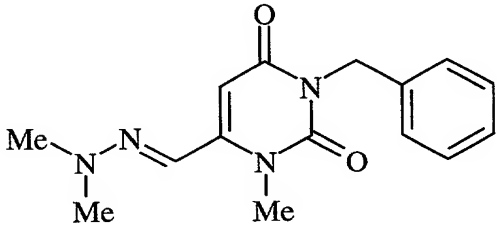
Consequently, a subject of the present invention is also a process for manufacturing a compound of genral formaula (I) in which X_1 and X_3 are CH, X_2 is N, Z is -NR_7 in which

R_7 is as defined in the compound of formual (I), W is O, and Y is O, characterized in that the said process comprises a step in which a compound of general (XXXII):



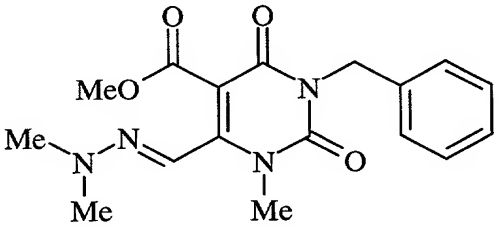
(XXXII)

is reacted in a first step with selenium dioxide in the presence of acetic acid, in a second step with dimethylhydrazine, and in a third step with N,N'-dimethylformamide dimethylacetal under reflux of DMF, to give a compound of formula (XXXIII):



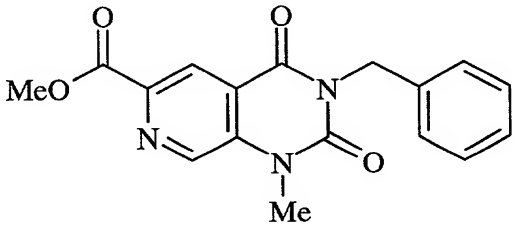
(XXXIII)

followed by reacting th compound of formula (XXXIII) whith methyl acrylate in the presence of palladium diacetate, to give the compound of general formula (XXXIV):



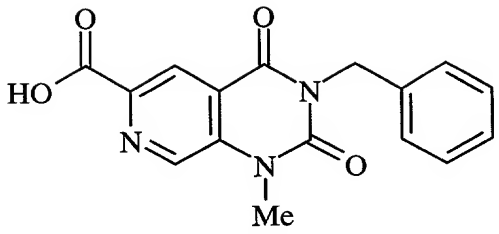
(XXXIV)

followed by reacting the compound of formula (XXXIV) whith chlorobenzene and acetic acid to give the compound of formula (XXXV):



(XXXV)

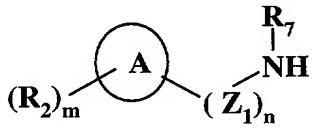
followed by reacting the compound of formula (XXXV) in the presence of a base to give the compound of general formula (XXXVI):



(XXXVI)

the said compound of formula (XXXVI) :

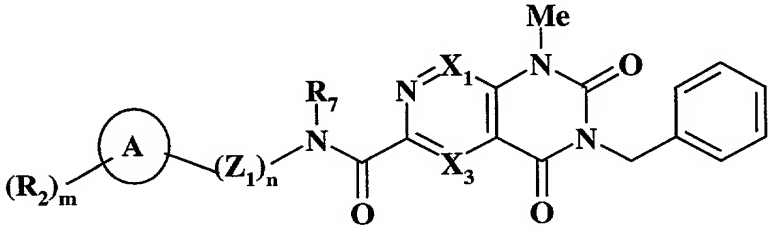
- either is reacted, in the presence of an acid activator such as TOTU, with the compound of formula (VII):



(VII)

in which R_7 is selected from hydrogen, $(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2, Z_1, m and n are as defined in the summary of the invention,

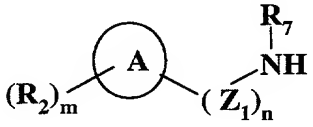
to give the compound of general formula (XXXVII):



(XXXVII)

in which A, R_2, R_7, Z_1, m and n are as defined hereinbefore, and X_1 and X_3 represents each -CH group,

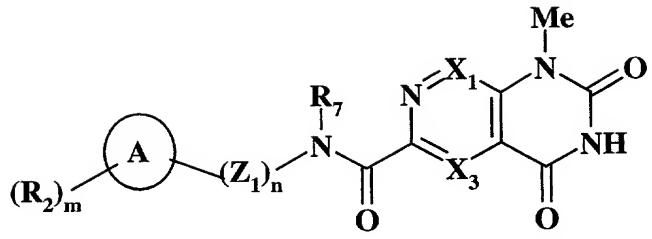
- or is reacted in a first step with $AlCl_3$ in the presence of benzene, and in a second step in the presence of an acid activator such as TOTU, with the compound of formula (VII):



(VII)

in which R_7 is selected from hydrogen, $(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2, Z_1, m and n are as defined in the summary of the invention,

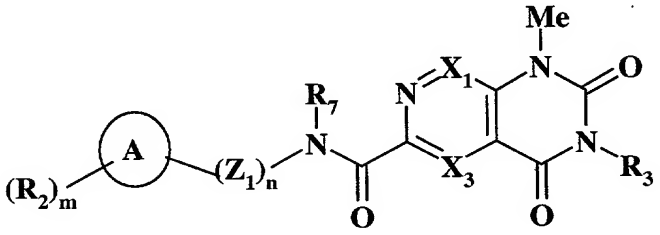
to give the compound of general formula (XXXVIII):



(XXXVIII)

in which A, R_2, R_7, Z_1, m and n are as defined hereinbefore, and X_1 and X_3 represents each -CH group,

followed by reacting the compound of formula (XXXVIII) with a compound of formula R_3-X in which R_3 is as defined in the compound of general formula (I), in the presence of a base, to give the compound of formula (XXXIX):



(XXXIX)

The present invention is also illustrated, without being limited thereby, in the examples which follow.

EXAMPLES:

Preparation A : Dimethyl 4-aminoisophthalate

Preparation according to Scheme 2:

Step 1-2 : 4-Nitroisophthalic acid

25 g (138 mmol) of 5-methyl-2-nitrobenzoic acid are suspended in 300 ml of water. 5 g (89.1 mmol) of KOH are added for dissolution. The medium is heated to 90°C and 158 g of $KMnO_4$ (414 mmol) are added portionwise, rinsing with H_2O. After 3 hours, the reaction medium is filtered through Celite and the filtrate is acidified to pH 1 with concentrated HCl. The precipitate obtained is filtered off and dried under vacuum.

Weight = 15.3 g ; **Yield** = 53%

NMR: DMSO ^1H δ (ppm) 5.62-5.70 (d,1H); 7.88 (d,1H); 8.16 (s,1H)

Step 2-2 : Dimethyl 4-nitroisophthalate

12.75 g (60.4 mmol) of 4-nitroisophthalic acid from the above stage and 13 ml of H_2SO_4 and 100 ml of methanol are maintained at reflux overnight. After cooling, the methanol is removed under vacuum. The residue is dissolved in 400 ml of EtOAc. The organic phase is washed with 50 ml of H_2O and then with 50 ml of 5% $NaHCO_3$ solution.

Drying over $MgSO_4$ and concentration under vacuum gives a crystalline residue.

Weight = 12.17 g **Yield** = 84%

NMR: DMSO ^1H δ (ppm) 3.86 (s,3H); 3.91 (s,3H); 8.16 (d,1H); 8.29-8.34 (m,2H)

Step 3-2: Dimethyl 4-aminoisophthalate

The compound from the above stage is reduced with hydrogen in the presence of palladium as catalyst.

Filtration through Celite and concentration gives:

Weight = 5.12 g **Yield** = 70%

m.p. = 127-128°C

NMR: $CDCl_3$ ^1H δ (ppm) 3.87 (s,3H); 3.88 (s,3H); 6.30 (brs,2H); 6.65 (d,1H); 7.89 (dd,1H); 8.57 (d,1H)

Preparation according to Scheme 3 - J. Org. Chem., 1997, 62 (12), 4088-4096

Step 1-3: Dimethyl 4-amino-1-hydroxycyclohexa-3,5-diene-1,3-dicarboxylate

526 ml of benzene and 250 ml of methyl acrylate are introduced into a 1-litre three-necked flask fitted with a reflux condenser, placed under inert atmosphere and protected from moisture, followed by 10 g (70.8 mmol) of methyl 5-amino-2-furan carboxylate. The mixture is brought to reflux and maintained for 24 hours. The reaction medium is concentrated to dryness on a rotavapor at 50°C under a vacuum of 20 mm Hg. The residue obtained is purified by flash chromatography using dichloromethane progressively enriched with ethyl acetate as solvent. The product is obtained as follows:

Weight = 15 g of a yellow precipitate **Yield** = 93%

TLC: CH_2Cl_2/EtOAc 70/30 v/v Rf = 0.35

m.p. = 101.3°C

NMR: $CDCl_3$ ^1H δ (ppm) 2.87 (d,1h); 2.93 (d,1H); 3.20 (s,1H); 3.71 (s,3H); 3.82 (s,3H); 6.02 (d,1H); 5.60-6.40 (brs,2H); 6.17 (d,1H)

Step 2-3 : Dimethyl 4-aminoisophthalate

15 g (66 mmol) of compound obtained in Step 1-3 and 600 ml of benzene are introduced into a 1-litre three-necked flask fitted with a reflux condenser, placed under an inert atmosphere and protected from moisture. 13.8 g (12 ml, 98 mmol) of BF_3 etherate are added with stirring. The mixture is refluxed for 2 minutes and then cooled to room temperature and, after addition of saturated $NaHCO_3$ solution (pH 9), the phases are separated by settling. The aqueous phase is re-extracted twice with dichloromethane. The organic phases are combined and dried over Na_2SO_4. After removal of the solvents under vacuum, the 13.8 g of residue are purified by chromatography using dichloromethane as elution solvent. The product is obtained as follows:

Weight = 8.5 g of a crystallyne residue **Yield** = 62%

TLC: CH_2Cl_2. Rf = 0.30

m.p. = 130.1°C

NMR: $CDCl_3$ ^1H δ (ppm) 3.87 (s,3H); 3.88 (s,3H); 6.30 (brs,2H); 6.65 (d,1H); 7.89 (dd,1H); 8.57 (d,1H)

Preparation B : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

Preparation according to Scheme 4:

Step 1-4 : Methyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylate

4 g (19.1 mmol) of compound of preparation A and 40 ml of pyridine are successively introduced into a 50 ml three-necked flask fitted with a reflux condenser and protected from moisture, followed by addition of 3.2 g (24 mmol) of benzyl isocyanate. The colourless solution is stirred and heated at 95-100°C. After 6 hours at this temperature, 1 ml of benzyl isocyanate is added and stirring is then continued at 100°C overnight. The

next day, the reaction medium is cooled and poured into 400 ml of a water + ice mixture, it is left stirring for about 30 minutes and the precipitate obtained is then filtered off. The product is re-slurried at reflux in 150 ml of ethanol. After cooling, the product is filtered off. The product is obtained as follows:

Weight = 3.7 g **Yield** = 62%

NMR: DMSO ^{1}H δ (ppm): 3.75 (s,3H); 4.95 (s,2H); 7.1-7.2 (m,6H); 8.05 (d,1H); 8.35 (s,1H); 11.8 (bs,1H)

Step 2-4 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

1.5 g (4.84 mmol) of methyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate, 14 ml of dioxane and 48 ml of H_2O are introduced into a 100 ml round-bottomed flask fitted with a reflux condenser. 0.41 g (9.68 mmol) of hydrated lithium hydroxide is added to the suspension with stirring. The mixture is brought to reflux and maintained for about 1 hour (solution). After cooling in an ice bath, the medium is acidified to pH 1 with concentrated hydrochloric acid. The very fine precipitate obtained is filtered off, to give:

Weight: 1.3 g **Yield** = 96%

NMR: DMSO ^{1}H δ (ppm): 5.1 (s,2H); 7.2-7.35 (m,6H); 8.15 (d,1H); 8.48 (s,1H); 11.85 (s,1H); 13.1 (bs,1H)

Preparation according to Scheme 5:

Step 1-5 : Dimethyl 4-(3-benzylureido)isophthalate

10 g (48 mmol) of compound of Preparation A, 200 ml of anhydrous toluene, about 100 mg of animal charcoal and then 12 g (40 mmol) of triphosgene are introduced into a 1-litre one-necked flask fitted with a reflux condenser and protected from moisture. The suspension is stirred and maintained at the reflux point of the toluene for 2 hours. The reaction medium is filtered through infusorial earth and then concentrated to dryness at 50°C under a vacuum of about 20 mm Hg. The residue obtained is dissolved in 200 ml of anhydrous toluene and stirred.

4.7 ml (43 mmol) of benzylamine are added to this solution over a few minutes. A precipitate is immediately formed. 200 ml of toluene are added to facilitate stirring, and the mixture is maintained at room temperature overnight. The next day, the precipitate is

filtered off and washed successively with toluene and ether. After drying under vacuum, the product is obtained as follows:

Weight 13.9 g **Yield** = 84.6%

TLC: CH_2Cl_2/acetone 98/2 Rf = 0.35

m.p. = 181.9°C

NMR: DMSO ^1H δ (ppm) 3.8 (s,3H); 3.9 (s,3H); 4.3 (s,2H); 7.2-7.4 (m,5H); 8.0 (d,1H); 8.3 (s,1H); 8.5 (s,1H); 8.55 (d,1H); 10.2 (s,1H)

Step 2-5 : Methyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylate

13.7 g (40 mmol) of compound obtained in Step 1-5, 300 ml of methanol and then 1.3 g (24 mmol) of sodium methoxide are introduced into a 1-litre one-necked flask fitted with a reflux condenser and protected from moisture. The white suspension is maintained at reflux for 3 hours (the suspension changes form). Half of the methanol is removed on a rotavapor at 50°C under vacuum. The mixture is cooled and acidified to pH 4 with 2 ml of concentrated hydrochloric acid. It is left stirring for 15 minutes while cold and the crystalline residue obtained is then filtered off.

Weight = 12 g **Yield** = 96.7%

TLC: CH_2Cl_2/acetone 98/2

Rf = 0.05-0.2

m.p. = 248.1°C

NMR: DMSO ^1H δ (ppm) 3.9 (s,3H); 5.1 (s,2H); 7.2-7.4 (m,6H); 8.15 (d,1H); 8.45 (s,1H); 11.9 (bs,1H)

Step 3-5 : 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

The product is obtained according to the procedure of Step 2-4 of Preparation B using the compound obtained in preceding Step 2-5.

Preparation according to Scheme 6:

Step 1-6 : 3-Benzyl-6-bromo-1*H*-quinazoline-2,4-dione

10 g (46.3 mmol) of 2-amino-5-bromobenzoic acid, 100 ml of anhydrous pyridine and 6.16 g (46.3 mmol) of benzyl isocyanate are introduced into a 250 ml one-necked flask

fitted with a reflux condenser and protected from moisture. The solution is maintained at reflux with stirring for 36 hours. The reaction mixture is cooled and H_2O is added until the start of precipitation. The mixture is left to crystallize for about 1 hour and the precipitate obtained is then filtered off and washed. The 8 g of crude product are purified by reslurrying in refluxing ethanol.

Weight: 3.4 g

NMR: = DMSO ^1H δ (ppm): 4.9 (s,2H); 7.0 (d,1H); 7.03-7.2 (m,5H); 7.65 (d,1H); 7.85 (s,1H); 11.5 (s,1H)

Step 2-6 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carbonitrile

2.5 g (7.5 mmol) of compound of Step 1-6, 1.215 g (13.6 mmol) of copper cyanide and 22.5 ml of 1-methyl-2-pyrrolidinone are introduced into a 50 ml three-necked flask fitted with a reflux condenser and protected from moisture. The beige-coloured solution obtained is refluxed at an internal temperature of 200°C for 1 h 30 min.

The reaction medium is concentrated to dryness at 80°C under a vacuum < 1 mm Hg. The residue is taken up in 300 ml of 2N NH_4OH and extracted 3 times with dichloromethane. The presence of an insoluble material is noted, this material being taken up twice in 20 ml of a 50/50 v/v MeOH/CH_2Cl_2 mixture. The organic phases are combined and washed with H_2O. After drying over Na_2SO_4 and concentration under vacuum, the black residue obtained is crystallized from 10 ml of CH_2Cl_2. The product is obtained as follows:

Weight: 1.2 g **Yield** = 60%

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.50

NMR: DMSO ^1H δ (ppm): 4.82 (s,2H); 6.97-7.12 (m,6H); 7.80 (d,1h); 8.1 (s,1H); 11.75 (bs,1H)

Step 3-6 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

1.4 g (5.05 mmol) of compound of Step 2-6 and 35 ml of H_2O are introduced into a 100 ml one-necked flask fitted with a reflux condenser, followed by cautious addition of 35 ml of H_2SO_4. The suspension is maintained at reflux with stirring for 3 hours.After cooling, the beige-coloured precipitate is filtered off and washed to neutrality with H_2O and then with methanol.

Weight: 1.5 g **Yield** = 100%

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.10

m.p. = 360°C

Preparation C : 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid

Step 1: Methyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylate

11.8 g (38.0 mmol) of Preparation B, 120 ml of dimethylformamide and 7.9 g (57 mmol) of K_2CO_3 are introduced into a 250 ml three-necked flask. The suspension is stirred for 15 minutes at room temperature. 27 g (12 ml, 190 mmol) of iodomethane are added over 2 minutes. The suspension is stirred at room temperature for 30 to 45 minutes. The solvent is removed under vacuum and the residue is taken up in 500 ml of dichloromethane and washed with 3 times 300 ml of water. The organic phase is dried and the solvent is removed. The product is obtained as follows:

Weight: 12 g **Yield** = 97.4%

TLC: CH_2Cl_2/acetone 98/2 Rf = 0.60

m.p. = 179.3°C

NMR: DMSO ^1H δ (ppm) 3.6 (s,3H); 3.90 (s,3H); 5.1 (s,2H); 7.2-7.4 (m,5H); 7.55 (d,1H); 8.25 (d,1H); 8.6 (s,1H)

Step 2: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

The product is obtained with a yield of 100% (10 g) according to the procedure of Step 2-4 of Preparation B using 9.5 g (29.3 mmol) of compound obtained in Step 1.

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.50

m.p. = 227.2°C

NMR: DMSO ^1H δ (ppm) 3.55 (s,3H); 5.15 (s,2H); 7.2-7.4 (m,5H); 7.55 (d,1H); 8.25 (d,1H); 8.6 (s,1H); 13.2 (bs,1H)

Preparation D: 1-Methyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

Step 1: Methyl 3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

5.5 g (26.3 mmol) of compound of the Preparation A and 50 ml of pyridine are introduced into a round-bottomed flask. 5.0g (33.1 mmol) of 3-fluorobenzyl isocyanate are added. The mixture is maintained at reflux for 6 hours and 0.8 g (5.3 mmol) of 3-fluorobenzyl isocyanate is added in one portion. The mixture is heated overnight at reflux. The mixture is cooled and the product is precipitated with the addition of water and filtered. The product is reslurryed in hot ethanol and filtered to provide 6.7 g (yield:78%) of the desired compound.

MS: m/z (APCI, AP+) 329.1 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 62.20; H, 3.99; N, 8.53.
Found (%) : C, 62.09; H, 3.85; N, 8.42.

Step 2: Methyl 1-methyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

1.8 g (5.5 mmol) of the product from the preceding Step 1 is dissolved in 30 ml of dimethylformamide and 1.8 g (8.1 mmol) of cesium carbonate is added. The mixture is stirred 10 minutes before adding iodomethane 1.1 g (8.1 mmol). Stirring is continued overnight at room temperature. Water (60 ml) is added and the product is extracted with ethyl acetate (2 x 30 ml). The organic extracts are combined and washed with saturated aqueous NaCl solution (4 x 20 ml), and dried $MgSO_4$. Slurried solid product in hot ethyl acetate and filtered to obtain 1.7 g (yield : 90%) of the desired compound.

MS: m/z (APCI, AP+) 343.1 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 63.16; H, 4.42; N, 8.18.
Found (%) : C, 63.02; H, 4.26; N, 8.06.

Step 3: 1-Methyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

0.71 g of the compound (yield:76%) is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the preceding Step 2.

MS: m/z (APCI, AP+) 329.0 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 62.20; H, 3.99; N, 8.53.
Found (%) : C, 61.94; H, 3.78; N, 8.57.

Preparation E: 1-Ethyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

Step 1: Methyl 1-ethyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

2.0 g (6.1 mmol) of the compound of Step 1 of Preparation D are dissolved in 30 ml of dimethylformamide and 1.96 g (9.2 mmol) of cesium carbonate is added. The mixture is stirred 10 minutes before adding 1.4 g (9.2 mmol) of iodoethane. Stirring is continued overnight at room temperature. Water (60 ml) is added and the product is extracted with ethyl acetate (2 x 30 ml). The organic extracts are combined and washed with saturated aqueous NaCl solution (4 x 20 ml), and dried $MgSO_4$. Slurried solid product in hot ethyl acetate and filtered to obtain 1.4 g (yield: 67%) of the desired compound.

MS: m/z (APCI, AP+) 357.1 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 64.04; H, 4.81; N, 7.86.
Found (%) : C, 63.72; H, 4.68; N, 7.75.

Step 2: 1-Ethyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

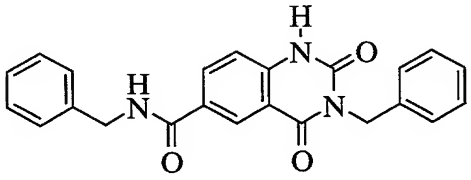
1.1 g of the compound (yield: 71%) is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the preceding Step 1.

MS: m/z (APCI, AP+) 343.0 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 63.16; H, 4.42; N, 8.18.
Found (%) : C, 63.06; H, 4.41; N, 8.03.

Examples 1 to 461 illustrate, without limiting it, the synthesis of particularly active compounds of formula (I) according to the invention.

Example 1: 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide



0.150 g (0.51 mmol) of compound of Preparation B and 8.0 ml of anhydrous dimethylformamide are introduced into a stirred 25 ml one-necked flask protected from moisture. 0.054 g (56 µl, 0.51 mmol) of benzylamine and 0.17 g (0.51 mmol) of TOTU are added to this solution. The solution is cooled in a bath to 0°C. 0.132 g (0.18 ml, 1.02 mmol) of N,N-diisopropylethylamine is then added. The mixture is warmed to room temperature and stirred overnight. After monitoring by TLC (90/10 CH_2Cl_2/MeOH), the DMF is removed under vacuum. The crystalline residue obtained is taken up in dichloromethane with the amount of methanol required for total dissolution. The organic phase is washed successively with 40 ml of 1N HCl, 40 ml of H_2O, 40 ml of saturated $NaHCO_3$ solution and finally 40 ml of H_2O. The organic phase is dried over Na_2SO_4 and the solvents are removed under vacuum. 0.140 g of product is obtained, which is recrystallized from 30 ml of acetonitrile:

Weight: 0.110 g **Yield** = 56%

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.65

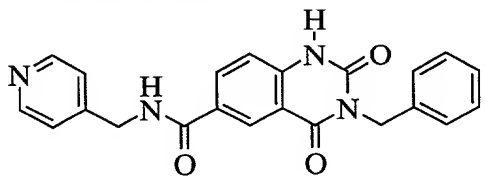
NMR: DMSO ^1H δ (ppm): 4.45 (d,2H); 5.1 (s,2H); 7.1-7.4 (m,11H); 8.1 (d,1H); 8.5 (s,1H); 9.15 (m,1H); 11.75 (bs,1H)

IR: 3425,2364,1722,1640,1509,1442,1304,1261,1078,927,845 cm^{-1}

m.p. = 241.2°C

HPLC: 98.3%

Example 2 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (4-pyridylmethyl)amide



The product is obtained with a yield of 46% (0.090 g) according to the procedure of Example 1 using 4-picolylamine, and after recrystallization from a 50/50 EtOAc/EtOH mixture.

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.60

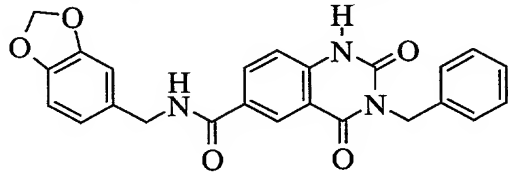
NMR: DMSO ^1H δ (ppm): 4.5 (d,2H); 5.1 (s,2H); 7.2-7.4 (m,8H); 8.15 (d,1H); 8.5 (d,2H); 8.55 (s,1H); 9.25 (t,1H); 11.75 (s,1H)

IR: 3250,1725,1669, 1642,1623,1450,1345,1301,1075,1006, 830 cm^{-1}

m.p. = 305.2°C

HPLC: 95.1%

Example 3 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



The product is obtained with a yield of 64% (0.140 g) according to the procedure of Example 1 using piperonylamine, and after crystallization from acetonitrile.

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.65

NMR: DMSO ^1H δ (ppm): 4.35 (d,2H); 5.1 (s,2H); 5.95 (s,2H);6.7-6.95 (m,3H); 7.15-7.4 (m,6H); 8.15 (d,1H); 8.5 (s,1H); 9.1 (t,1H); 11.7 (bs,1H)

IR: 3200,1727,1636, 1493,1444,1299,1261,1041,938,841,763,726 cm^{-1}

m.p. = 256°C

HPLC: 99%

Example 4: 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-thienylmethyl)amide

The product is obtained with a yield of 40% (0.080 g) according to the procedure of Example 1, but using 2-thienylmethylamine, and after a crystallization from acetonitrile.

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.65

NMR: DMSO ^1H δ (ppm): 4.35 (d,2H); 4.85 (s,2H); 6.7-6.85 (m,2H); 6.95-7.2 (m,7H); 7.9 (d,1H); 8.3 (s,1H); 9.05 (t,1H); 11.55 (bs,1H)

IR: 1729,1637,1511,1444,1346,1298,1261,1072,845,763 cm^{-1}

m.p. = 236.3°C

HPLC: 98.7%

Example 5 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (3-pyridylmethyl)amide

The product is obtained with a yield of 66% (0.130 g) according to the procedure of Example 1, but using 3-(aminomethyl)-pyridine, and after a crystallization from acetonitrile.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.40

NMR: DMSO ^1H δ (ppm): 4.5 (d,2H); 5.15 (s,2H); 7.15-7.4 (m,7H); 7.7 (d,1H); 8.15 (d,1H); 8.45 (d,1H); 8.55 (d,2H); 9.25 (t,1H); 11.8 (s,1H)

IR: 3345,1716,1670,1638,1621,1450,1433,1348,1298,1068,829,774 cm^{-1}

m.p. = 252.3°C

HPLC: 97.4%

Example 6: 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide

The product is obtained with a yield of 47.2% (0.100 g) according to the procedure of Example 1, but using 4-methoxybenzylamine, and after a crystallization from acetonitrile.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.45

NMR: DMSO ^1H δ (ppm): 3.7 (s,3H); 4.4 (d,2H); 5.1 (s,2H); 6.9 (d,2H); 7.2-7.4 (m,8H); 8.15 (d,1H); 8.5 (s,1H); 9.15 (t,1H); 11.8 (bs,1H)

IR: 3400,3210,1727,1638,1513,1441,1300,1253,1173,1040,843, 760 cm^{-1}

m.p. = 269°C

HPLC: 100%

Example 7: 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-chlorobenzylamide

The product is obtained with a yield of 19% (0.040 g) according to the procedure of Example 1, but using 4-chlorobenzylamine, and after a crystallization from acetonitrile.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.45

NMR: DMSO ^1H δ (ppm): 4.5 (d,2H); 5.1 (s,2H); 7.2-7.45 (m,10 H); 8.15 (d,1H); 8.5 (s,1H); 9.25 (t,1H); 11.8 (bs,1H)

IR: 3365,3200,1726,1638,1551,1512,1444,1305,1263,1012,844, 763 cm^{-1}

m.p. = 280.6°C

HPLC: 98.1%

Example 8: 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methylbenzylamide

The product is obtained with a yield of 19% (0.040 g) according to the procedure of Example 1, but using 4-methylbenzylamine, and after a crystallization from acetonitrile.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.40

NMR: DMSO ^1H δ (ppm): 2.3 (s,3H); 4.4 (d,2H); 5.1 (s,2H); 7.0-7.4 (m,10H); 8.15 (d,1H); 8.55 (s,1H); 9.1 (t,1H); 11.8 (bs,1H)

IR: 3280,1720,1671,1640,1623,1550,1278,848,774,744 cm^{-1}

m.p. = 267.8°C

HPLC: 98.7

Example 9: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

0.500 g (1.61 mmol) of compound of Preparation C in 25 ml of anhydrous dimethylformamide are introduced into a stirred 50 ml one-necked flask protected from moisture. 0.244 g (0.201 ml, 1.61 mmol) of piperonylamine and 0.531 g (1.61 mmol) of TOTU are added to this solution. The solution is cooled in a cold bath to 0°C. 0.415 g

(0.564 ml, 3.22 mmol) of N,N-diisopropylethylamine is then added. The mixture is warmed to room temperature and stirred overnight.

After monitoring by TLC (90/10 CH_2Cl_2/MeOH), DMF is removed under vacuum. The crystalline residue obtained is taken up in dichloromethane. The organic phase is washed successively with 1N HCl, H_2O, saturated $NaHCO_3$ and finally H_2O. The organic phase is dried over Na_2SO_4 and the solvent is removed under vacuum. 0.540 g of product, recrystallized from 30 ml of acetonitrile, is obtained as follows:

Weight: 0.390 g **Yield** = 54.6%

TLC: CH_2Cl_2/acetone 90/10 Rf = 0.40

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 4.35 (d,2H); 5.15 (s,2H); 6.0 (s,2H); 6.75-6.95 (m,3H); 7.2-7.4 (m,5H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H)

IR: 3303,1703,1656,1637,1498,1444,1322,1254,1040,932,845 cm^{-1}

m.p. = 215.1°C

HPLC: 99.5%

Example 10: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide

The product is obtained with a yield of 56.8% (0.110 g) according to the procedure of Example 9, but using benzylamine, and after a crystallization from acetonitrile.

TLC: CH_2Cl_2/acetone 90/10 Rf = 0.55

NMR: $CDCl_3$ ^1H δ (ppm) 3.65 (s,3H); 4.65 (d,2H); 5.3 (s,2H); 6.55 (m,1H); 7.2-7.6 (m,11H); 8.3 (d,1H); 8.5 (s,1H);

IR: 1708,1655,1641,1616,1507,1478,1326,1246,930,750 cm^{-1}

m.p. = 198.9°C

HPLC: 100%

Example 11: Methyl 4-({[1-(3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)methanoyl]amino}methyl)benzoate

The product is obtained with a yield of 61.5% (0.135 g) according to the procedure of Example 9, but using methyl 4-(aminomethyl)benzoate hydrochloride and 3.5 equivalents

of N,N-diisopropylethylamine. The crude product is purified by chromatography on silica, using a 95/5 CH_2Cl_2/MeOH gradient, followed by a solidification in ether.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.36

NMR: DMSO ^1H δ (ppm) : 3.55 (s,3H); 3.85 (s,3H); 4.55 (d,2H); 5.15 (s,2H); 7.2-7.35 (m,5H); 7.45 (d,2H); 7.6 (d,1H); 7.95 (d,2H); 8.3 (d,1H); 8.65 (s,1H); 9.35 (t,1H)

IR:1723,1706,1657,1642,1617,1506,1477,1284,1109,749 cm^{-1}

m.p. = 196°C

HPLC: 100%

Example 12: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-hydroxy-3-methoxybenzylamide

The product is obtained with a yield of 42% (0.090 g) according to the procedure of Example 9, but using 4-hydroxy-3-methoxybenzylamine hydrochloride and 3.5 equivalents of N,N-diisopropylethylamine. The crude product is purified by chromatography on silica, using a 95/5 CH_2Cl_2/MeOH gradient, followed by a solidification in ether.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.59

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.75 (s,3H); 4.4 (d,2H); 5.15 (s,2H); 6.75 (s,2H); 6.95 (s,1H); 7.2-7.40 (m,6H); 7.55 (d,1H); 8.3 (d,1H); 8.65 (s,1H); 8.8 (s,1H); 9.15 (t,1H)

IR: 1707,1655,1618,1502,1477,1277,704 cm^{-1}

m.p. = 183°C

HPLC: 87.1%

Example 13: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide

The product is obtained with a yield of 77.7% (0.320 g) according to the procedure of Example 9, but using 4-methoxybenzylamine. The crude product is purified by chromatography on silica, using 97/3 CH_2Cl_2/MeOH as eluent. The desired fractions are combined and concentrated. The product is solidified in ether and then filtered off

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.8

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.75 (s,3H); 4.45 (d,2H); 5.2 (s,2H); 6.9 (d,2H); 7.2-7.4 (m,7H); 7.6 (d,1H); 8.3 (d,1H); 8.65 (s,1H); 9.25 (t,1H)

IR: 1705,1660,1636,1505,1251,750 cm^{-1}

m.p. = 191°C

HPLC: 97.3%

Example 14: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (4-pyridylmethyl)amide

The product is obtained with a yield of 67.7% (0.130 g) according to the procedure of Example 9, but using 4-picolylamine.

The crude product is purified by chromatography on silica, using 95/5 CH_2Cl_2/MeOH as eluent. The desired fractions are combined and concentrated. The product is solidified in ether and then filtered off.

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.18

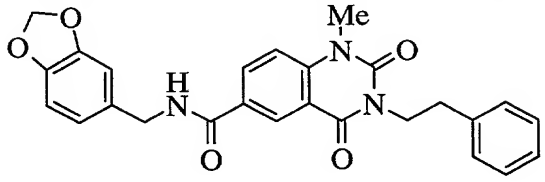
NMR: DMSO ^1H δ (ppm): 3.60 (s,3H); 4.55 (d,2H); 5.15 (s,2H); 7.2-7.4 (m,7H); 7.6 (d,1H); 8.3 (d,1H); 8.5 (d,2H); 8.65 (s,1H); 9.35 (t,1H)

IR: 1705,1658,1634,1508,1332,831,749,705 cm^{-1}

m.p. = 172°C

HPLC: 98.8%

Example 15: 1-Methyl-2,4-dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



Step 1: Methyl 2,4-dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylate

0.750 g (3.6 mmol) of compound of Preparation A and 7.5 ml of pyridine are introduced into a round-bottomed flask. 0.530 g (0.5 ml; 3.6 mmol) of phenethyl isocyanate is added.

The mixture is maintained at 100°C overnight. Since the reaction is incomplete, a second addition of phenethyl isocyanate, i.e. 2 equivalents, is carried out. After precipitation with H_2O, filtration and purification by reslurrying in hot ethanol, the product is obtained as follows:

Weight:0.640 g **Yield** = 54.9%

NMR: DMSO ^1H δ (ppm): 2.85-2.95 (m,2H); 4.90 (s,3H); 4.05-4.15 (m,2H); 7.15-7.3 (m,6H); 8.15 (d,1H); 8.45 (s,1H); 11.8 (bs,1H)

Step 2: 2,4-Dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

The product from the preceding step is hydrolysed to the acid according to the procedure of Step 2-4 of Preparation B to provide 0.500 g of the desired compound (yield :80%).

NMR: DMSO ^1H δ (ppm) 2.85-2.95 (m,2H); 4.05-4.15 (m,2H); 7.15-7.3 (m,6H); 8.15 (d,1H); 8.45 (s,1H); 11.75 (s,1H); 13.05 (bs,1H)

Step 3: 2,4-Dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 57.8% (0.205g) according to the procedure of Example 1, using 250 mg (0.8 mmol) of the compound obtained in the preceding Step 2 and piperonylamine.

NMR: DMSO ^1H δ (ppm): 2.9 (t,2H); 4.1 (t,2H); 4.4 (d,2H); 5.95 (s,2H); 6.75-6.95 (m,3H); 7.15-7.35 (m,6H); 8.1 (d,1H); 8.5 (s,1H); 9.1 (t,1H); 11.65 (bs,1H)

IR: 3249,1704,1658,1636,1488,1251,810,753 cm^{-1}

m.p. = 296°C

HPLC: 99.5%

Step 4: 1-Methyl-2,4-dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

0.190 g (0.46 mmol) of the product from the preceding Step 3, 2 ml of dimethylformamide and 0.095 g (0.68 mmol) of K_2CO_3 are introduced into a 25 ml round-bottomed flask. The mixture is stirred for 15 min at room temperature and 0.325 g (0.15 ml, 2.29 mmol) of iodomethane is then added. Stirring is continued for 30 to 45 minutes. The solvent is

removed under vacuum. The residue is taken up in dichloromethane and washed with H_2O. The organic phase is separated out after settling and dried over Na_2SO_4. After concentration under vacuum, the product is purified by chromatography on silica, using a 98/2 CH_2Cl_2/MeOH gradient, and then solidified in ether to provide 0.080g of the desired compound (yield : 76%).

NMR: DMSO ^{1}H δ (ppm): 2.9 (t,2H); 3.55 (s,3H); 4.15 (t,2H); 4.4 (d,2H); 5.95 (s,2H); 6.8-6.95 (m,3H); 7.15-7.35 (m,5H); 7.55 (d,1H); 8.25 (d,1H); 8.6 (s,1H); 9.15 (t,1H)

IR: 3272,1705,1664,1635,1501,1254,1041,751,698 cm^{-1}

m.p. = 183°C

HPLC: 99.7%

Example 16: 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

Step 1: Methyl 3-(4-methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

The product is obtained with a yield of 61.3% (0.750g) according to the procedure of Step 1 of Example 15, but using 4-methoxybenzyl isocyanate:

NMR: DMSO ^{1}H δ (ppm): 3.7 (s,3H); 3.8 (s,3H); 5.0 (s,2H); 6.8-6.85 (m,2H); 7.2-7.3 (m,3H); 8.1-8.2 (m,1H); 8.5 (s,1H); 11.9 (bs,1H)

Step 2: 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

The product from the preceding Step 1 is hydrolysed to the acid according to the procedure of Step 2-4 of Preparation B to provide 0.680 g of the desired compound (yield :94.8%).

NMR: DMSO ^{1}H δ (ppm): 3.7 (s,3H); 5.0 (s,2H); 6.8-7.9 (m,2H); 7.2-7.3 (m,3H); 8.1-8.2 (m,1H); 8.5 (s,1H); 11.8 (s,1H); 13.1 (bs,1H)

Step 3: 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 79.9% (0.220g) according to the procedure of Example 9, using 200 mg (0.6 mmol) of the compound obtained in the preceding Step 2 and piperonylamine. The crude product is solidified in dichloromethane.

NMR: DMSO ^{1}H δ (ppm): 3.7 (s,3H); 4.35 (d,2H); 5.0 (s,2H); 5.95 (s,2H); 6.75-6.9 (m,5H); 7.2-7.3 (m,3H); 8.1 (d,1H); 8.5 (s,1H); 9.1 (t,1H); 11.75 (s,1H)

IR: 1720,1648,1634,1504,1442,1300,1250,1036,766 cm^{-1}

m.p. = 252°C

HPLC: 96.2%

Example 17: 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The alkylation with methyl iodide of the product obtained in Example 16 is carried out using the procedure described in Example 15, Step 4. After crystallization from ether, 0.080 g of the product is obtained (yield : 70.4%).

NMR: DMSO ^{1}H δ (ppm): 3.55 (s,3H); 3.7 (s,3H); 4.4 (d,2H); 5.05 (s,2H); 5.95 (s,2H); 6.8-6.95 (m,5H); 7.3 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.6 (s,1H); 9.2 (t,1H)

IR: 3265,1704,1662,1634,1504,1443,1320,1248,1040,771 cm^{-1}

m.p. = 178°C

HPLC: 99.2%

Example 18: 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid 4-methoxybenzylamide

Step 1: 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (4-methoxybenzyl)amide

The product is obtained with a yield of 82% (0.270g) according to the procedure of Example 9, using 240 mg (0.74 mmol) of the compound obtained in Step 2 of Example 16 and 4-methoxybenzylamine

NMR: DMSO ^{1}H δ (ppm): 3.7 (2s,6H); 4.4 (d,2H); 5.0 (s,2H); 6.8-6.95 (m,4H); 7.2-7.35 (m,5H); 8.15 (d,2H); 8.5 (s,1H); 9.15 (t,1H); 11.75 (bs,1H)

Step 2: 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide

The product is obtained with a yield of 94.4% (0.260g) according to the procedure of Example 15 Step 4, using the compound obtained in the preceding in Step 1.

NMR: DMSO ^{1}H δ (ppm): 3.6 (s,3H); 3.7 (dd,6H); 4.45 (d,2H); 5.1 (s,2H); 6.8-6.95 (m,4H); 7.25-7.40 (m,4H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H)

IR: 1705,1655,1641,1614,1510,1247,1175,1033 cm^{-1}

m.p. = 195°C

HPLC: 99.5%

Example 19: 3-(1-Naphth-1-ylethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained according to the procedure of Example 16, Step 1 to 3, using 1-(1-naphthyl)ethyl isocyanate in the Step 1.

NMR: DMSO ^{1}H δ (ppm): 1.95 (d,3H); 4.35 (d,2H); 6.0 (s,2H); 6.7-6.8 (m,2H); 6.8-6.9 (m,2H); 7.2 (d,1H); 7.4-7.5 (m,2H); 7.6 (t,1H); 7.85-8.0 (m,5H); 8.10 (d,1H); 8.45 (s,1H); 9.10 (t,1H); 11.6 (bs,1H)

Example 20: 2,4-Dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

Step 1: Dimethyl 4-(3-pyrid-4-ylmethylureido)isophthalate

The product is obtained with a yield of 94.2% according to the procedure of Step 1-5 of Preparation B, using the compound obtained in the Preparation A and 4-pyridine methylamine.

NMR: DMSO ^{1}H δ (ppm): 3.8 (s,3H); 3.9 (s,3H); 4.3 (d,2H); 7.30-7.35 (m,2H); 8.0-8.1 (m,1H); 8.4 (t,1H); 8.5-8.6 (m,4H); 10.3 (s,1H)

Step 2: Methyl 2,4-dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-

carboxylate

The product is obtained according to the procedure of Step 2-5 of Preparation B, using the compound obtained in the preceding Step 1.

NMR: DMSO ^{1}H δ (ppm): 3.85 (s,3H); 5.1 (s,2H); 7.20-7.30 (m,3H); 8.2 (d,1H); 8.4-8.5 (m,3H); 11.95 (bs,1H)

Step 3: 2,4-Dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

The product is obtained according to the procedure of Step 2-4 of Preparation B, using the compound obtained in the preceding Step 2.

NMR: DMSO ^{1}H δ (ppm): 5.1 (s,2H); 7.20-7.30 (m,3H); 8.2 (d,1H); 8.4-8.5 (m,3H); 11.9 (s,1H); 13.1 (bs,1H)

Step 4: 2,4-Dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 26.7% (0.850 g) according to the procedure of Example 1, using the compound obtained in the preceding Step 3 and piperonylamine. After filtering off an insoluble material, the dimethylformamide is removed under vacuum. The residue is solidified in dichloromethane.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.40

NMR: DMSO ^{1}H δ (ppm): 4.40 (d,2H); 5.0 (s,2H); 5.95 (s,2H); 6.80-6.9 (m,3H); 7.20-7.30 (m,3H); 8.1-8.2 (m,1H); 8.4-8.5 (m,3H); 9.1 (t,1H); 11.8 (s,1H)

IR: 3267,1713,1645,1626,1444,1313,1040,920,769 cm^{-1}

m.p. = 291.2°C

HPLC: 87.7%

Example 21: 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide

Step 1: Methyl N-benzyl-6-(3-thien-2-ylmethylureido)isophthalate

The product is obtained according to the procedure of Step 1-5 of Preparation B, using the compound obtained in the Preparation A and 2-thiophene methylamine.

NMR: DMSO ^{1}H δ (ppm): 3.8 (s,3H); 3.9 (s,3H); 4.5 (d,2H); 6.9-7.0 (m,2H); 7.4 (m,1H); 8.0-8.05 (m,1H); 8.4 (t,1H); 8.5 (s,1H); 8.6-8.65 (m,1H); 10.15 (s,1H)

Step 2: Methyl 2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylate

The product is obtained according to the procedure of Step 2-5 of Preparation B, using the compound obtained in the preceding Step 1.

NMR: DMSO ^{1}H δ (ppm): 3.8 (s,3H); 5.25 (s,2H); 6.9 (d,1H); 7.1 (s,1H); 7.25 (d,1H); 7.4 (d,1H); 8.1-8.15 (m,1H); 8.5 (s,1H); 11.9 (bs,1H)

Step 3: 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

The product is obtained according to the procedure of Step 2-4 of Preparation B, using the compound obtained in the preceding Step 2.

NMR: DMSO ^{1}H δ (ppm): 5.25 (s,2H); 6.95 (d,1H); 7.15 (d,1H); 7.2-7.3 (m,1H); 7.4 (d,1H); 8.1-8.2 (m,1H); 8.5 (s,1H); 11.9 (s,1H); 13.1 (bs,1H)

Step 4: 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide

The product is obtained with a yield of 61.9% (0.160 g) according to the procedure of Example 1, using the compound obtained in the preceding Step 3 and benzylamine.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.8

NMR: DMSO ^{1}H δ (ppm): 4.50 (d,2H); 5.2 (s,2H); 6.90-7.4 (m,9H); 8.15 (d,1H); 8.6 (s,1H); 9.2 (t,1H); 11.8 (s,1H)

IR: 3185,1730,1646,1633,1512,1446,1292,1260,845,763 cm^{-1}

m.p. = 264.8°C

HPLC: 99.5%

Example 22: 1-Methyl-2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid benzylamide

The product is obtained with a yield of 87% (0.090 g) according to the procedure of Step 4 of Example 15, using the compound obtained in the Example 21.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.8

NMR: DMSO ^1H δ (ppm): 3.6 (s,3H); 4.50 (d,2H); 5.3 (s,2H); 6.90-7.0 (m,1H); 7.2-7.5 (m,7H); 7.55 (d,1H); 8.3 (d,1H); 8.7 (s,1H); 9.25 (t,1H)

IR: 3257,1704,1657,1637,1513,1480,1325,1251,829,787 cm^{-1}

m.p. = 223.7°C

HPLC: 99.9%

Example 23: 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 59% (0.170 g) according to the procedure of Example 1, using the compound obtained in Step 3 of Example 21 and piperonylamine. The crude product is solidified in dichloromethane:

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.4

NMR: DMSO ^1H δ (ppm): 4.40 (d,2H); 5.25 (s,2H); 6.0 (s,2H); 6.75–7.0 (m,4H); 7.1 (s,1H); 7.25 (d,1H); 7.40 (d,1H); 8.2 (d,1H); 8.55 (s,1H); 9.20 (t,1H); 11.8 (s,1H)

IR: 3185,1727,1632,1502,1445,1300,1259,1040,936,846,765 cm^{-1}

m.p. = 270.1°C

HPLC: 95.2%

Example 24: 1-Methyl-2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 79.7% (0.085 g) according to the procedure of Step 4 of Example 15, using the compound obtained in the Example 23.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.8

NMR: DMSO ^1H δ (ppm): 3.6 (s,3H); 4.40 (d,2H); 5.30 (s,2H); 6.0 (s,2H); 6.8–7.0 (m,4H); 7.2 (d,1H); 7.40 (d,1H); 7.5-7.6 (m,1H); 8.2-8.30 (m,1H); 8.6 (s,1H); 9.20 (t,1H)
IR: 3251,1705,1659,1635,1501,1446,1328,1253,1041,926,784 cm^{-1}
m.p. = 224.2°C
HPLC: 99.8%

Example 25: 3-(4-Chlorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 67.8% (0.170 g) according to the procedure of Example 15 Steps 1 to 3, using in the first step the compound obtained in the Preparation A and 4-chlorobenzyl isocyanate. The product is obtained after solidification in dichloromethane.
NMR: DMSO ^1H δ (ppm): 4.35 (t,2H); 5.1 (s,2H); 5.95 (s,2H); 6.75-6.9 (m,3H); 7.25 (d,1H); 7.35 (s,4H); 8.15 (d,1H); 8.5 (s,1H); 9.15 (t,1H); 11.8 (bs,1H)
IR: 3265,1734,1653,1633,1504,1440,1254,1041,811,761 cm^{-1}
m.p. = 290°C
HPLC: 99.2%

Example 26: 3-(4-Chlorobenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 88.9% (0.085 g) according to the procedure of Example 15 Step 4, using the compound obtained in Example 25. The product is isolated after crystallization in ether.
NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 4.40 (t,2H); 5.15 (s,2H); 5.95 (s,2H); 6.75-6.9 (m,3H); 7.35 (s,4H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H)
IR: 3249,1704,1658,1636,1488,1251,810,753 cm^{-1}
m.p. = 231°C
HPLC: 99.6%

Example 27: 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained (0.035 g) according to the procedure of Example 20 Steps 1 to 4, using in the first step the compound obtained in the Preparation A and monomethylamine, and in Step 4, piperonylamine for the amidation.

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.50

NMR: DMSO ^1H δ (ppm): 3.35 (s,3H); 3.55 (s,3H); 4.40 (d,2H); 6.0 (s,2H); 6.75-6.95 (m,3H); 7.55 (d,1H); 8.25 (d,1H); 8.6 (s,1H); 9.25 (t,1H)

IR: 1703,1649,1501,1486,1256,1037,923 cm^{-1}

m.p. = 279°C

HPLC: 97.3%

Example 28: 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 36% (0.040 g) according to the procedure of Example 20 Steps 1 to 4, using in the first step the compound obtained in the Preparation A and piperonylamine, and in Step 4, piperonylamine for the amidation.

Step 1: Dimethyl 4-(3-benzo[1,3]dioxol-5-ylmethylureido)isophthalate

NMR: CDCl3 ^1H δ (ppm): 3.9 (s,6H); 4.4 (s,2H); 5.1 (t,1H); 6.70–6.85 (m,3H); 6.95 (s,2H); 8.1-8.2 (m,1H); 8.6-8.7 (m,2H); 10.6 (bs,1H)

Step 2: Methyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

NMR: DMSO ^1H δ (ppm): 3.8 (s,3H); 5.0 (s,2H); 5.9 (s,2H); 6.8 (s,2H); 6.9 (s,1H); 7.25 (d,1H); 8.15 (d,1H); 8.5 (s,1H); 11.8 (bs,1H)

Step 3: 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

NMR: DMSO ^1H δ (ppm): 5.0 (s,2H); 6.0 (s,2H); 6.8 (s,2H); 6.9 (s,1H); 7.3 (d,1H); 8.2 (d,1H); 8.5 (s,1H); 11.85 (s,1H); 13.05 (bs,1H)

Step 4: 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

TLC: CH_2Cl_2/MeOH 95/5

Rf = 0.70

NMR: DMSO ^1H δ (ppm): 4.40 (s,2H); 5.0 (s,2H); 5.9 (s,4H); 6.75-6.95 (m,6H); 7.20-7.30 (m,1H); 8.05-8.15 (m,1H); 8.45-8.55 (m,1H); 9.1 (m,1H); 10.3 (m,1H)

IR: 3271,1739,1649,1630,1503,1440,1250,1041,926,759 cm^{-1}

m.p. = 245.2°C

HPLC: 81.5%

Example 29: 3-(Benzo[1,3]dioxol-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 40.5% (0.050 g) according to the procedure of Example 15 Step 4, using the compound obtained in the Example 28.

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.80

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 4.35 (s,2H); 5.0 (s,2H); 6.0 (s,4H); 6.80-7.0 (m,6H); 7.5 (d,1H); 8.25 (d,1H); 8.6 (s,1H); 9.15-9.2 (m,1H)

IR: 3302,1703,1663,1630,1490,1247,1041,929,807,785 cm^{-1}

m.p. = 197.5°C

HPLC: 100%

Example 30: 3-Benzyl-1-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

0.150 g (0.35 mmol) of compound of Example 2, and then 3 ml of anhydrous DMF are introduced into a stirred round-bottomed flask protected from moisture. 0.075 g

(0.525 mmol) of K_2CO_3 is added to the stirred solution. The mixture is stirred for 15 minutes and 0.273 g (0.14 ml, 1.75 mmol) of iodoethane is then added. Stirring is continued for about 1 hour. After removing the solvent under vacuum, the residue is dissolved in 50 ml of dichloromethane and washed with 2x 50 ml of H_2O. After drying over Na_2SO_4 and concentration under vacuum, the product is crystallized from 8 ml of acetonitrile. The product is obtained as follows:

Weight: 0.070 g **Yield** = 43.7%

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.70

NMR: DMSO ^1H δ (ppm): 1.25 (t,3H); 4.2 (q,2H); 4.4 (d,2H); 5.15 (s,2H); 5.95 (s,2H); 6.75-6.95 (m,3H); 7.2-7.4 (m,5H); 7.65 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.15 (t,1H)

IR: 1701,1658,1633,1506,1488,1458,1246,1217,1038,926,803 cm^{-1}

m.p. = 176.5°C

HPLC: 99%

Example 31: 3-Benzyl-1-cyclopropylmethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 76.8% (0.130 g) according to the procedure of Example 30, using cyclopropylmethyl bromide. The product is obtained after solidification in diisopropyl ether.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.70

NMR: DMSO ^1H δ (ppm): 0.4-0.55 (m,4H); 1.25 (m,1H); 4.1 (d,2H); 4.35 (d,2H); 5.15 (s,2H); 5.95 (s,2H); 6.85 (m,3H); 7.3 (m,5H); 7.7 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H)

IR: 1703,1656,1641,1504,1467,1307,1261,1241,1043,936,845,748 cm^{-1}

m.p. = 184.4°C

HPLC: 97.2%

Example 32: 3-Benzyl-1-isobutyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 35.3% (0.060 g) according to the procedure of Example 30, using isobutyl bromide.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.65

NMR: CDCl3 ^1H δ (ppm): 1.0 (d,6H); 2.15 (m,1H); 4.0 (d,2H); 4.5 (d,2H); 4.25 (s,2H); 5.95 (s,2H); 6.55 (m,1H); 6.8 (m,3H); 7.25 (m,4H); 7.45 (d,2H); 8.25 (t,1H); 8.45 (s,1H)

IR: 1705,1660,1643,1548,1502,1456,1303,1260,1245,1043,923 cm^{-1}

m.p. = 146.0°C

HPLC: 96.8%

Example 33: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

Step 1: Methyl 1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

0.870 g (2.7 mmol) of compound obtained in Step 1 of Preparation C, 20 ml of benzene and 2.1 g (16.1 mmol) of $AlCl_3$ are maintained at 50°C for 7 hours. After cooling, the medium is precipitated on a water/ice mixture. The insoluble material is dissolved in dichloromethane and purified by flash chromatography, eluting with a gradient of CH_2Cl_2/acetone. 0.510 g of the desired compound is obtained

Step 2: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The saponification of the compound obtained in the preceding Step 1 is carried out with LiOH in a dioxane/H_2O mixture as for the preceding examples. Amidation with piperonylamine gives 0.160 g of the desired product.

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.45

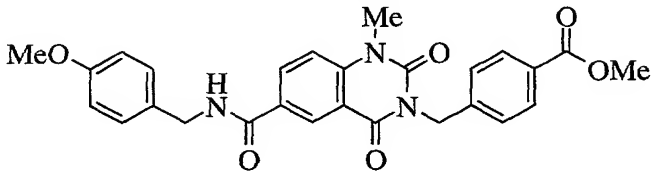
NMR: DMSO ^1H δ (ppm) 3.45 (s,3H); 4.4 (d,2H); 6.0 (s,2H); 6.75-6.95 (m,3H); 7.5 (d,1H); 8.25 (d,1H); 8.55 (s,1H); 9.2 (t,1H); 11.7 (s,1H)

IR: 3290,1697,1635,1503,1484,1324,1258,1040,844 cm^{-1}

m.p. = 279°C

HPLC: 98.7%

Example 34: Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate



Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide:

Preparation identical to that of Example 33, using 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (**NMR**: DMSO ^{1}H δ (ppm) 3.50 (s,3H); 7.5 (d,1H); 8.20 (d,1H); 8.50 (s,1H); 11.75 (bs,1H); 13.1 (bs,1H)) and 4 methoxy-benzylamine in DMF with TOTU and DIPEA. The product is obtained as follows:

NMR: DMSO ^{1}H δ (ppm) 3.50 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.20 (d,1H); 8.55 (s,1H); 9.20 (t,1H); 11.65 (bs,1H);

Step 2: Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

0.8 g (2.36 mmoles) of the product obtained in the preceding Step 1 and 8 ml anhydrous DMF are stirred with 1.15 g (3.54 mmol) of cesium carbonate. Stirring is continued for 15 minutes and then 0.81 g (3.54 mmol) of methyl-4-(bromomethyl)benzoate is added.The mixture is maintained at 90°C for 1h15min and then stirred overnight. 15ml of water are added and then extracted with dichloromethane. The organic phase is washed with water and concentrated to dryness on a rotavapor. The product obtained is purified with flash chromatography eluting with a gradient of CH_2Cl_2/MeOH to provide 0.220 g of the desired product.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.85

NMR: DMSO ^{1}H δ (ppm): 3.55 (s,3H); 3.7 (s,3H); 3.85 (s,3H); 4.4 (d,2H); 5.25 (s,2 H); 6.9 (d,2H); 7.25 (d,2H); 7.45 (d,2H); 7.55 (d,1H); 7.9 (d,2H); 8.25 (dd,1H); 8.6 (s,1H); 9.2 (t,1H)

IR : 3387,1709,1658,1642,1508,1286,1248,1110,1032,835,750 cm^{-1}

m.p = 189.2 °C

HPLC : 96.5 %

Example 35: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*] -quinazolin-3-ylmethyl]-benzoic acid

0.16g (3.3 mmoles) of the product obtained in Example 34 is hydrolysed in a mixture of 1.2 ml of dioxane and 4.2 ml of water with 28mg of LiOH monohydrate. The mixture is maintained at reflux for 10 minutes to complete the reaction. After acidification at pH 1 with concentrated HCl, the precipitate is filtered off to provide 0.120 g of the desired compound.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.50

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.75 (s,3H); 4.4 (d,2H); 5.20 (s,2 H); 6.9 (d,2H); 7.25 (d,2H); 7.40 (d,2H); 7.60 (d,1H); 7.85 (d,2H); 8.25 (dd,1H); 8.65 (s,1H); 9.2 (t,1H) 12.9 (bs,1H)

IR : 3378,1702,1658,1645,1616,1506,1297,1248,1125,839,788,751 cm^{-1}

m.p = 262.5 °C

HPLC : 100 %

Example 36: 1-Methyl-2,4-dioxo-3-((E)-3-phenylallyl)-1,2,3,4-tetrahydroquinazoline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

0.100 g (0.28 mmol) of compound of Example 33 and 1 ml of anhydrous DMF are stirred with 0.060 g (0.42 mmol) of K_2CO_3. The mixture is maintained for 15 min, followed by addition of 0.085 g (0.42 mmol) of cinnamyl bromide. The mixture is maintained at 70°C for 2 hours. After concentration under vacuum, the residue is taken up in dichloromethane, washed with H_2O and then dried over Na_2SO_4. The solvent is removed and the product is purified by flash chromatography, eluting with a 95/5 gradient of CH_2Cl_2/MeOH. A solidification in ether provides 0.070 g (yield=51%) of the desired compound.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.46

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 4.4 (d,2H); 4.75 (d,2H); 6.0 (s,2H); 6.3-6.4 (m,1H); 6.6 (d,1H); 6.80-6.95 (m,3H); 7.2-7.35 (m,3H); 7.4 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.25 (t,1H)

IR: 1659,1643,1503,1477,1246,754 cm^{-1}

m.p. = 174°C

HPLC: 98.4%

Example 37: Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

A mixture of 0.5 g (1.7 mmol) of the compound of Preparation B, 0.44 g (1.7 mmol) of triphenylphosphine and 0.44 ml (4.3 mmol) of benzyl alcohol is stirred in 20 ml of THF. A solution of 0.27 ml (1.7 mmol) of DEAD in 10 ml of THF is added dropwise with stirring. Stirring is continued overnight at room temperature. The precipitate formed is filtered through Celite and the filtrate is concentrated under vacuum. The residue is dissolved in 50 ml of ethyl acetate and washed successively with H_2O and then with saturated NaCl solution. After drying over $MgSO_4$ and concentration under vacuum, the crude product obtained is purified by flash chromatography on silica, eluting with a 50/50 mixture of hexane/EtOAc. The desired fractions are combined and the solvent is removed under vacuum to provide 0.190 g (yield = 29%) of the desired crystalline compound.

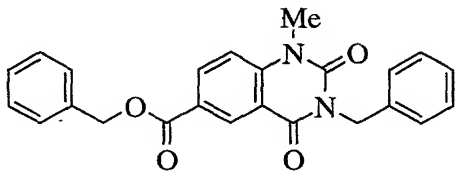
MS: m/z 387.2 (M+H)+

NMR: DMSO ^1H δ (ppm): 5.06 (s,2H); 5.34 (s,2H); 7.22-7.46 (m,10H); 8.20 (d,1H); 8.48 (s,1H); 11.89 (s,1H)

CHN ($C_{23}H_{18}N_2O_4$) calc (%) : C = 71.49, H = 4.70, N = 7.25

Found (%): C = 71.28, H = 4.94, N = 7.11

Example 38: Benzyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylate



0.084 g (0.217 mmol) of the product of Example 37 is stirred with anhydrous THF in apparatus protected from moisture and under an inert atmosphere. 0.14 ml of 1.6M BuLi in hexane (0.224 mmol) is introduced. The mixture is stirred for 10 minutes, followed by addition of 0.04 ml (0.642 mmol) of methyl iodide. The THF is removed under vacuum. The residue is dissolved in EtOAc and washed successively with H_2O and then with

saturated NaCl solution. After drying over $MgSO_4$ and concentration under vacuum, the crude product obtained is purified by flash chromatography on silica, eluting with a 50/50 mixture of hexane/EtOAc. The desired fractions are combined and the solvent is removed under vacuum. The pale yellow product is solidified in ether:

Weight: 0.049 g **Yield** = 56% MS: m/z 401.2 (M+H)+

NMR: DMSO ^1H δ (ppm): 3.31 (s,3H); 5.12 (s,2H); 5.37 (s,2H); 7.21-7.60 (m,11H); 8.28 (d,1H); 8.58 (s,1H)

CHN ($C_{24}H_{20}N_2O_4$) calc (%): C = 71.99, H = 5.03, N = 7.00

Found (%): C = 71.71, H = 5.25, N = 6.87

Example 39: 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylate

The compound is obtained according to the procedure of Example 37, but using dichloromethane as solvent, the product is obtained as follows:

MS: m/z 388.2 (M+H)+

NMR: DMSO ^1H δ (ppm): 5.07 (s,2H); 5.41 (s,2H); 7.20-7.32 (m,6H); 7.43 (d,2H); 8.26 (d,1H); 8.53-8.58 (m,3H); 11.93 (s,1H)

CHN ($C_{22}H_{17}N_3O_4$. $0.3H_2O$) calc (%): C = 67.27, H = 4.52, N = 10.70

found (%): C = 67.32, H = 4.40, N = 10.47

Example 40: 4-Pyridylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4 -tetrahydroquinazoline -6-carboxylate

The compound is obtained according to the procedure of Example 37, but using the compound of Preparation C and 4-pyridylcarbinol.

MS: m/z 402.3 (M+H)+

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 5.14 (s,2H); 5.42 (s,2H); 7.23-7.33 (m,5H); 7.43-7.45 (m,2H); 7.60 (d,1H); 8.32-8.36 (m,1H); 8.57-8.64 (m,3H)

CHN ($C_{23}H_{19}N_3O_4$. 0.14 H_2O): calc (%): C = 68.39, H = 4.81, N = 10.40

found (%): C = 68.40, H = 4.71, N = 10.38

Example 41: Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

0.100 g (0.337 mmol) of compound of Preparation B and 1 ml of anhydrous THF are placed in a round-bottomed flask protected from moisture. The suspension is stirred and 0.24 g (0.150 ml, 2.025 mmol) of thionyl chloride is added. The mixture is refluxed for 1 h 30 min. After cooling, the solution is concentrated to dryness on a rotavapor. The 0.110 g of acid chloride obtained is used in the next stage without further purification.

0.080 g (0.51 mmol) of piperonyl alcohol, 1 ml of dichloromethane and 0.051 g (0.070 ml, 0.51 mmol) of triethylamine are introduced into a round-bottomed flask protected from moisture. The solution is cooled to 0°C.

The above acid chloride suspended in 2.5 ml of dichloromethane is added to the solution. The mixture is stirred at room temperature for 48 hours. The precipitate obtained is filtered off. The 0.050 g is purified by recrystallization from acetonitrile.

Weight: 0.025 g **Yield** = 17%

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.85

NMR: DMSO ^1H δ (ppm): 5.1 (s,2H); 5.25 (s,2H); 6.05 (s,2H); 6.9-7.4 (m,9H); 8.2 (d,1H); 8.5 (s,1H); 11.9 (bs,1H)

IR: 1715,1650,1624,1446,1285,1262,1080,928,865,764 cm^{-1}

m.p. = 238.5°C

HPLC: 99.7%

Example 42: Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

The compound is obtained (0.140 g) according to the procedure of Example 41, but using the compound of Preparation C and piperonyl alcohol.

TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.85

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 5.15 (s,2H); 5.30 (s,2H); 6.05 (s,2H); 6.9-7.4 (m,8H); 7.6 (d,1H); 8.25 (d,1H); 8.6 (s,1H)

IR: 1716,1703,1659,1618,1447,1294,1227,1103, 935,813,763 cm^{-1}

m.p. = 199.5°C

HPLC: 98.8%

Example 43: Benzyl 1-benzyl-2,4-dioxo-3-pyrid-4-ylmethyl-1,2,3,4 -tetrahydroquinazoline-6-carboxylate

0.5 g (1.7 mmol) of compound obtained in the Step 3 of Example 20 in 15 ml of anhydrous THF is stirred and 0.2 ml (1.7 mmol) of benzyl chloride and 1.2 g (8.7 mmol) of K_2CO_3 are added. The mixture is stirred overnight at room temperature and treated as usual to provide the desired compound.

MS: m/z 478.2 (M+H)+

NMR: DMSO ^{1}H δ (ppm): 5.19 (s,2H); 5.35 (s,2H); 5.39 (s,2H); 7.25-7.45 (m,13H); 8.19 (d,1H); 8.47-8.49 (m,2H); 8.62 (s,1H)

CHN ($C_{29}H_{23}N_3O_4$) calc (%): C = 72.94, H = 4.85, N = 8.80

Found (%): C = 72.58, H = 4.79, N = 8.57

Example 44: 4-Pyridylmethyl 2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4 -tetrahydroquinazoline-6-carboxylate

0.69 g (2.3 mmol) of compound obtained in Step 3 of Example 21 is treated according to the procedure of Example 37, using 4-pyridylcarbinol. The product is obtained as follows:

MS: m/z 394.2 (M+H)+

NMR: DMSO ^{1}H δ (ppm): 5.21 (s,2H); 5.40 (s,2H); 6.93 (d,1H); 7.11 (m,1H); 7.28 (d,1H); 7.40 (d,1H); 7.40 (m,2H); 8.24 (d,1H); 8.49-8.59 (m,3H)

CHN ($C_{20}H_{15}N_3O_4S \cdot 0.13\ CH_2Cl_2 \cdot 0.03$ (ether))

Calc (%): C = 59.81 H = 3.86, N = 10.33;

Found (%): C = 59.79, H = 3.82, N = 10.32

Example 45: 4-Pyridylmethyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4 -tetrahydroquinazoline-6-carboxylate

The compound is obtained (0.040 g) according to the procedure of example 37, but using the compound obtained in the Step 3 of Example 28 and 4-pyridylcarbinol. The product is crystallized from methanol:

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.70

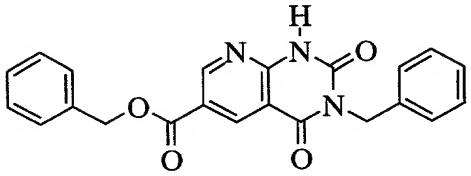
NMR: DMSO ^1H δ (ppm): 5.0 (s,2H); 5.70 (s,2H); 6.0 (s,2H); 6.85 (s,2H); 7.0 (s,1H); 7.4 (d,1H); 7.95-8.05 (m,2H); 8.3-8.35 (m,1H); 8.60 (s,1H); 8.8-8.95 (m,2H); 12.0 (m,1H)

IR: 1710,1670,1622,1501,1440,1279,1236,1041,923;764 cm^{-1}

m.p. = 204.4°C

HPLC: 92.4%

Example 46: Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine -6-carboxylate



Step 1: 3-Benzyl-6-methyl-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione

20 g (111 mmol) of ethyl 2-amino-5-methylnicotinate and 200 ml of pyridine are brought to reflux. 13.7 ml (111 mmol) of benzyl isocyanate are added. Refluxing is continued overnight. After cooling, the precipitate is filtered off and washed with 2x100 ml of ethanol and 2x 100 ml of ether.

Weight: 10 g in two crops **Yield** = 34%

TLC: CH_2Cl_2/MeOH 90/10 Rf = 0.5

NMR: DMSO ^1H δ (ppm): 2.2 (s,3H); 5.0 (s,2H); 7.15-7.35 (m,5H); 8.1 (s,1H); 8.5 (s,1H)

m.p. = 279°C

HPLC: 97%

Step 2: 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylic acid

3.0 g (11.2 mmol) of the product of the preceding Step 1, 100 ml of H_2O, 7.1 g (44.9 mmol) $KMnO_4$ and 10 ml of NMP are introduced into a round-bottomed flask. The reaction medium is refluxed overnight. The medium is filtered while hot. The filtrate

crystallizes after cooling. After filtering off the new precipitate, the filtrate is treated with 40 ml of Amberlite IR 120 (+) resin. The resin and acid mixture is filtered and the acid is extracted by washing with a 70/30 mixture of CH_2Cl_2/MeOH. The solvent is removed under vacuum to provide 0.32 g of a white solid (yield = 10%).

NMR: DMSO ^1H δ (ppm): 5.0 (s,2H); 7.15-7.25 (m,5H); 8.65 (s,1H); 9.1 (s,1H); 12.4 (s,1H)

Step 3: Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylate

The esterification of the compound of the preceding Step 2 is carried out by the procedure described in Example 37, using benzyl alcohol.

After solidification in methanol, 0.040 g of the desired product is obtained (yield = 31%):

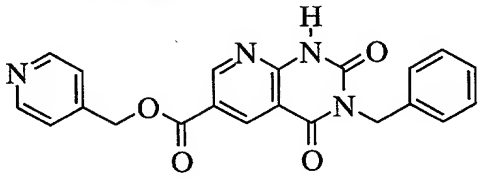
TLC: CH_2Cl_2/MeOH 95/5 Rf = 0.8

NMR: $CDCl_3$ ^1H δ (ppm): 5.2 (s,2H); 5.4 (s,2H); 7.2-7.6 (m,10H); 9.05 (s,1H); 9.3 (s,1H); 10.9 (s,1H)

m.p. = 223°C

HPLC: 93.1%

Example 47: 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*] pyrimidine-6-carboxylate.



The compound is obtained with a yield of 20% (0.050 g) according to the procedure described in Example 37, but using the compound obtained in the Step 2 of example 46 and 4-pyridylcarbinol.

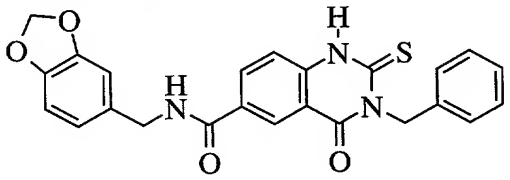
TLC: EtOAc/NH_4OH 99/1 Rf = 0.6

NMR: DMSO ^1H δ (ppm): 5.05 (s,2H); 5.4 (s,2H); 7.15-7.41 (m,5H); 7.45 (d,2H); 8.55 (d,2H); 8.7 (s,1H); 9.15 (s,1H); 12.55 (s,1H)

m.p. = 280°C

HPLC: 97%

Example 48: 3-Benzyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



The synthesis is carried out according to Synthetic Scheme 1, using benzyl isothiocyanate during the cyclization to the 4-oxo-2-thioxoquinazoline. After saponification and amidation with piperonylamine, the expected compound is obtained.

Weight: 0.100 g **TLC**: CH_2Cl_2/MeOH 95/5 Rf = 0.64

NMR: DMSO ^1H δ (ppm): 4.4 (d,2H); 5.65 (s,2H); 5.95 (s,2H); 6.75-6.95 (m,3H); 7.2-7.4 (m,5H); 7.45 (d,1H); 8.2 (d,1H); 8.55 (s,1H); 9.2 (t,1H); 13.2 (bs,1H)

IR: 1698,1636,1619,1528,1446,1194,1037,768

m.p. = 249°C

HPLC: 97.2%

Example 49: 4-[6-(4-Hydroxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

Into a stirred round-bottomed flask protected from moisture, 0.7 g (1.44 mmol) of compound of Example 34 and 70 ml of anhydrous dichloromethane are introduced. The mixture is stirred and 1.4 ml (14.4 mmol) of BBr_3 in 7 ml of dichloromethane are added dropwise. After 2 hours of stirring at room temperature the reaction is complete. After an usual treatment, 0.280 g of the desired product is obtained (yield = 42%).

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.15

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 4.35 (d,2H); 5.2 (s,2H); 6.65 (d,2H); 7.10 (d,2H); 7.40 (d,2H); 7.55 (d,1H); 7.85 (d,2H); 8.25 (d,1H); 8.60 (s,1H); 9.15 (t,1H); 9.2 (s,1H); 12.8 (bs,1H)

IR : 3403, 2553, 1697, 1658, 1615, 1507, 1482, 1423, 1247, 1109, 829, 752 cm^{-1}

M.P. = 174.0 °C

HPLC : 97.06 %

Example 50 : 3-(4-Dimethylcarbamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro quinazoline-6-carboxylic acid 4-methoxy-benzylamide

0.3 g (0.64 mmol) of the compound of Example 35 is treated with a 2M solution of dimethylamine in THF according to the procedure described in Example 1. The crude product is purified by chromatography on silica gel and concretized in ether to provide 0.160 g of the desired compound (yield : 49.9%).

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.70

NMR:.CDCl3 ^1H δ (ppm): 2.90 (s,3H); 3.05 (s,3H); 3.60 (s,3H); 3.80 (s,3H); 4.60 (d,2H); 5.25 (s,2H); 6.60 (t,1H); 6.85 (d,2H); 7.3 (m,5H); 7.45 (d,2H); 8.25 (d,1H); 8.50 (s,1H).

IR : 3378, 1710, 1654, 1641, 1618, 1508, 1476, 1246, 752 cm^{-1}

M.P. = 189 °C

HPLC : 97 %

Example 51 : 1-Methyl-3-(4-methylcarbamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro -quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of Example 50 but using methylamine.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.55

NMR: DMSO ^1H δ (ppm): 2.75 (d,3H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.85 (d,2H); 7.25 (d,2H); 7.35 (d,2H); 7.55 (d,1H); 7.75 (d,2H); 8.25 (q,1H); 8.35 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 3338, 1708, 1654, 1616, 1548, 1507, 1329, 1245, 1036, 825, 751 cm^{-1}

M.P. = 255.1 °C

HPLC : 97.0 %

Example 52: 3-Allyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-allyl bromide.

NMR: DMSO ^{1}H δ (ppm): 3.55 (s,3H); 3.8 (s,3H); 4.4 (d,2H); 4.55 (d,2H); 5.10-5.20 (m,2H); 5.80-5.95 (m,1H); 6.9 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.6 (s,1H); 9.25 (t,1H)

IR : 1703, 1642, 1615, 1508, 1477, 1246, 765 cm^{-1}

M.P. = 207 °C

HPLC : 98.9 %

Example 53 : 1-Methyl-2,4-dioxo-3-(2-pyrrol-1-yl-ethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 1(2-bromoethyl)pyrrole.

NMR: DMSO ^{1}H δ (ppm): 3.55 (s,3H); 3.7 (s,3H); 4.15 (m,2H); 4.25 (m,2H); 4.40 (d,2H); 5.90 (s,2H); 6.7 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.55 (s,1H); 9.2 (t,1H)

IR : 3338, 1708, 1655, 1640, 1508, 1478, 1251, 117, 1032, 835, 734 cm^{-1}

M.P. = 147 °C

HPLC : 96.6 %

Example 54: 1-Methyl-2,4-dioxo-3-(prop-2-ynyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and prp-2-ynyl bromide.

NMR: DMSO ^{1}H δ (ppm): 3.15 (s,1H); 3.55 (s,3H); 3.7 (s,3H); 4.40 (d,2H); 4.70 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.25 (t,1H).

IR : 3265, 1710, 1667, 1635, 1501, 1326, 1249, 1036, 825, 783, 752 cm^{-1}

M.P. = 206 °C

HPLC : 97.7 %

Example 55: 1-Methyl-3-(3-methyl-but-2-enyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 1-bromo-3-methyl-but-2-ene.

NMR: DMSO ^1H δ (ppm): 1.65 (s,3H); 1.75 (s,3H); 3.50 (s,3H); 3.7 (s,3H); 4.40 (d,2H); 4.55 (d,2H); 5.20 (t,1H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.25 (t,1H)

IR : 3282, 1705, 1659, 1634, 1500, 1314, 1246, 826 cm^{-1}

M.P. = 187 °C

HPLC : 96.9 %

Example 56: 1-Methyl-2,4-dioxo-3-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 2-(bromomethyl)pyridine.

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.7 (s,3H); 4.40 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (m,3H); 7.35 (d,1H); 7.60 (d,1H); 7.70 (m,1H); 8.25 (d,1H); 8.40 (d,1H); 8.60 (s,1H); 9.2 (t,1H)

IR : 1702, 1658, 1643, 1618, 1508, 1476, 1331, 1248, 751 cm^{-1}

M.P. = 156 °C

HPLC : 99.5 %

Example 57: 3-Carbamoylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 2-chloro-acetamide.

NMR: DMSO ^{1}H δ (ppm): 3.55 (s,3H); 3.7 (s,3H); 4.40 (d,2H); 4.50 (s,2H); 6.90 (d,2H); 7.20 (s,1H); 7.25 (d,2H); 7.55 (d,1H); 7.65 (s,1H); 8.25 (d,1H); 8.60 (s,1H); 9.25 (t,1H)

IR : 1655,1531,1508,1477,1303,1249,752 cm^{-1}

M.P. = 269 °C

HPLC : 99.2 %

Example 58: 1-Methyl-2,4-dioxo-3-(pyridin-3-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-(bromomethyl)pyridine.

NMR: DMSO ^{1}H δ (ppm): 3.55 (s,3H); 3.7 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.85 (d,2H); 7.20-7.40 (m,3H); 7.55 (d,1H); 7.75 (d,1H); 8.25 (m,1H); 8.45 (d,1H);8.60 (m,2H); 9.20 (t,1H)

IR : 1699, 1660, 1615, 1500, 1479, 1249, 1032, 752, 712 cm^{-1}

M.P. = 140 °C

HPLC : 89.6 %

Example 59 : 1-Methyl-3-(1-methyl-piperidin-3-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydro -quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-bromomethyl-1-methyl-piperidine

NMR: DMSO ^1H δ (ppm): 0.85-1.00 (m,1H); 1.30-1.45 (m,1H); 1.55-2.05 (m,5H); 2.10 (s,3H); 2.60 (m,2H); 3.55 (s,3H); 3.75 (s,3H); 3.85 (d,2H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.25 (t,1H)

IR : 2926, 1655, 1641, 1508, 1247, 788 cm^{-1}

M.P. = 174 °C

HPLC : 99.3 %

Example 60 :3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-(bromomethyl)benzonitrile

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.75 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.45-7.60 (m,3H); 7.75 (d,2H); 8.25 (d,1H); 8.60 (s,1H); 9.20 (t,1H)

IR : 3411, 2216, 1708, 1649, 1616, 1251, 839, 765 cm^{-1}

M.P. = 222 °C

HPLC : 97.2 %

Example 61 :3-(3-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-(bromomethyl)-benzonitrile.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.80

NMR: DMSO ^1H δ (ppm) : 3.45 (s,3H); 3.70 (s,3H); 4.45 (d,2H); 5.15 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (m,2H); 7.70 (m,2H); 7.80 (s,1H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H).

IR : 1708, 1660, 1618, 1503, 1477, 1335, 1247, 1160, 952, 760, 718 cm^{-1}

M.P. = 201 °C

HPLC : 97.1 %

Example 62 : 3-(2-Methoxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 1-bromo-2-methoxy-ethane.

NMR: DMSO ^{1}H δ (ppm): 3.25 (s,3H); 3.55 (m,5H); 3.70 (s,3H); 4.15 (t,2H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.20 (t,1H)

IR : 3274, 1709, 1660, 1633, 1514, 1249, 1030, 823 cm^{-1}

M.P. = 200 °C

HPLC : 99.2 %

Example 63 :3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline -6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-(bromomethyl)-1-methoxyphenyl.

NMR: DMSO ^{1}H δ (ppm): 3.55 (s,3H); 3.70 (s,6H); 4.40 (d,2H); 5.10 (s,2H); 6.75-6.90 (m,5H); 7.15-7.30 (m,3H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.20 (t,1H)

IR : 3387, 1704, 1657, 1640, 1616, 1509, 1250, 766 cm^{-1}

M.P. = 154 °C

HPLC : 99.4 %

Example 64: 3-Cyclopropylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline -6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and bromomethylcyclopropyl.

NMR: DMSO ^{1}H δ (ppm): 0.40 (m,4H); 1.2 (m,1H); 3.55 (s,3H); 3.70 (s,3H); 3.85 (d,2H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (m,1H); 8.60 (d,1H); 9.20 (t,1H).

IR : 3282,1703, 1657, 1634, 1502, 1258, 1028, 829, 752 cm^{-1}

M.P. = 209 °C

HPLC : 98.2 %

Example 65: 1-Methyl-3-(2-morpholin-4-yl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-(2-bromoethyl)morpholine.

NMR: DMSO ^{1}H δ (ppm): 2.40 (m,4H); 2.55 (m,2H); 3.50 (m,7H); 3.75 (s,3H); 4.10 (t,2H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.20 (t,1H)

IR : 3419, 1707, 1656, 1612, 1506, 1475, 1246, 1111, 752 cm^{-1}

M.P. = 135 °C

HPLC : 98.5 %

Example 66: 3-Cyclohexylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and (bromomethyl)cyclohexane.

NMR: DMSO ^{1}H δ (ppm): 0.9-1.20 (m,5H); 1.5-1.85 (m,6H); 3.55 (s,3H); 3.70 (s,3H); 3.80 (d,2H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.25 (m,1H); 8.60 (s,1H); 9.20 (t,1H)

IR : 3378, 2918, 1703, 1654, 1640, 1508, 1478, 1329, 1244, 789, 767 cm^{-1}

M.P. = 183 °C

HPLC : 99.0 %

Example 67: 1-Methyl-2,4-dioxo-3-(3-phenyl-propyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-phenylpropyl bromide.

NMR: DMSO ^{1}H δ (ppm): 1.90 (m,2H); 2.65 (t,2H); 3.50 (s,3H); 3.70 (s,3H); 4.0 (t,2H); 4.40 (d,2H); 6.85 (d,2H); 7.10-7.30 (m,7H); 7.50 (d,1H); 8.20 (m,1H); 8.60 (s,1H); 9.20 (t,1H).

IR : 3395, 1704, 1641, 1615, 1509, 1477, 1327, 1245, 1032, 749 cm^{-1}

M.P. = 167 °C

HPLC : 98.8 %

Example 68: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-(bromomethyl)-fluorobenzene.

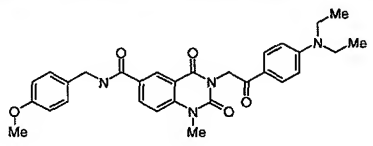
NMR: DMSO ^{1}H δ (ppm) : 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.1 (s,2H); 6.90 (d,2H); 7.10 (t,2H); 7.25 (d,2H); 7.40 (m,2H); 7.50 (d,1H); 8.25 (m,1H); 8.60 (s,1H); 9.20 (t,1H)

IR : 3395, 1704, 1641, 1615, 1509, 1477, 1327, 1245, 1032, 749 cm^{-1}

M.P. = 180 °C

HPLC : 99.4 %

Example 69: 3-[2-(4-Diethylamino-phenyl)-2-oxo-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide



The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 2-Chloro-1-(4-diethylamino-phenyl)-ethan-1-one.

NMR: DMSO ^{1}H δ (ppm): 1.15(t,6H); 3.30-3.50 (m,4H); 3.60(s,3H); 3.75 (s,3H); 4.45 (d,2H); 5.35 (s,2H); 6.75 (d,2H); 6.90 (d,2H); 7.30 (d,2H); 7.65 (d,1H); 7.90 (d,2H); 8.30 (m,1H); 8.60 (s,1H); 9.25 (t,1H)

IR : 3370, 1670, 1655, 1596, 1504, 1258, 1242, 1190, 808 cm^{-1}

M.P. = 237 °C

HPLC : 97.0 %

Example 70: Ethyl [6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-acetate

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and ethyl 2-chloro-acetate.

NMR: DMSO ^{1}H δ (ppm): 1.20 (t,3H); 3.60 (s,3H); 3.70 (s,3H); 4.15 (q,2H); 4.40 (d,2H); 4.70 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.60 (d,1H); 8.30 (m,1H); 8.60 (s,1H); 9.20 (t,1H)

IR : 1711, 1668, 1637, 1508, 1247, 1212, 1032, 835, 752 cm^{-1}

M.P. = 170 °C

HPLC : 97.7 %

Example 71: 3-(2-Hydroxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 2-bromoethan-1-ol.

NMR: DMSO ^{1}H δ (ppm): 3.50-3.65 (s,5H); 3.70 (s,3H); 4.05 (t,2H); 4.40 (d,2H);4.80 (t,1H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (s,1H); 8.25 (m,1H); 8.60 (s,1H); 9.25 (t,1H)

IR : 3290, 1702, 1654, 1639, 1619, 1509, 1327, 1240, 1071, 835, 753 cm^{-1}

M.P. = 168 °C

HPLC : 96.7 %

Example 72: Methyl 3-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-propionate

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 3-bromo-propanoate.

NMR: DMSO ^{1}H δ (ppm) : 2.60 (t,2H); 3.50 (s,3H); 3.60 (s,3H); 3.70 (s,3H); 4.20 (t,2H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.25 (dd,1H); 8.60 (s,1H); 9.25 (t,1H)

IR : 3411, 2361, 1704, 1656, 1644, 1618, 1508, 1478, 1328, 1244, 853, 766 cm^{-1}

M.P. = 154.8 °C

HPLC : 95.1 %

Example 73 :3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-propionic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B, but using as substrates the compound obtained in the Example 72.

TLC : CH_2Cl_2 / MeOH 90/10 Rf =.0.25

NMR: DMSO ^{1}H δ (ppm) : 2.50 (t,2H); 3.55 (s,3H); 3.70 (s,3H); 4.15 (t,2H); 4.40 (d,2H); 6.85 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.25 (dd,1H); 8.55 (s,1H); 9.15 (t,1H); 12.3 (bs,1H)

IR : 3395, 2353, 1701, 1656, 1639, 1508, 1478, 1244, 1040, 839, 799, 754 cm^{-1}

M.P. = 201.5 °C

HPLC : 96.4 %

Example 74 :Ethyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-butyrate

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and ethyl 4-bromobutyrate.

NMR: DMSO ^{1}H δ (ppm) : 1.10 (t,3H); 1.90 (q,2H); 2.30 (t,2H); 3.55 (s,3H); 3.70 (s,3H); 4.00 (bs,4H); 4.45 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.20 (dd,1H); 8.60 (s,1H); 9.15 (t,1H)

IR : 3378, 2943, 1704, 1657, 1647, 1617, 1509, 1477, 1246, 1178, 1030, 751 cm^{-1}

M.P. = 138.9 °C

HPLC : 99.1 %

Example 75 : 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-butyric acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B, but using as substrates the compound obtained in the Example 74.

TLC : CH_2Cl_2 / MeOH 90/10 Rf =.0.50

NMR: DMSO ^{1}H δ (ppm) : 1.80 (q,2H); 2.25 (t,2H); 3.50 (s,3H); 3.70 (s,3H); 4.0 (t,2H); 4.40 (d,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.25 (dd,1H); 8.60 (s,1H); 9.20 (t,1H); 12.0 (bs,1H)

IR : 3346, 1691, 1651, 1637, 1512, 1234, 1248, 1178, 1024, 835, 752 cm^{-1}

M.P. = 165.6 °C

HPLC : 99.1 %

Example 76: Methyl {4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-acetate

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 4-(bromomethyl)phenyl acetate

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.80

NMR: DMSO ^{1}H δ (ppm) : 3.55 (s,3H); 3.60 (s,3H); 3.65 (s,2H); 3.70 (s,3H); 4.40 (d,2H); 5.15 (s,2H); 6.90 (d,2H); 7.10-7.35 (m,6H); 7.55 (d,1H); 8.25 (dd,1H); 8.65 (s,1H); 9.20 (t,1H)

IR : 3370, 2951, 1707, 1655, 1639, 1616, 1509, 1328, 1251, 1157, 1036, 766 cm^{-1}

M.P. = 173.2 °C

HPLC : 99.0 %

Example 77 : {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-acetic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B, but using as substrates the compound obtained in the Example 76.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.50

NMR: DMSO ^{1}H δ (ppm) : 3.55 (s,2H); 3.60 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.15 (s,2H); 6.90 (d,2H); 7.10-7.35 (m,6H); 7.55 (d,1H); 8.25 (dd,1H); 8.60 (s,1H); 9.20 (t,1H); 12.3 (bs,1H)

IR : 3378, 1706, 1653, 1640, 1616, 1508, 1330, 1249, 1149, 1032, 823, 766 cm^{-1}

M.P. = 165 °C

HPLC : 96.7 %

Example 78 : 3-(4-Dimethylcarbamoylmethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained from the compound obtained in Example 77, which is transformed in situ into the acid chloride derivate by action of oxalyle chloride and then treated with a 2M solution of dimethylamine in THF.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.50

NMR: DMSO ^{1}H δ (ppm) : 2.80 (s,3H); 3.0 (s,3H); 3.55 (s,3H); 3.60 (s,2H); 3.75 (s,3H); 4.40 (d,2H); 5.15 (s,2H); 6.90 (d,2H); 7.15 (d,2H); 7.25 (d,4H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H).

IR : 3308, 2926, 1706, 1665, 1640, 1504, 1474, 1320, 1250, 1133, 1036, 834 cm^{-1}

M.P. = 183 °C

HPLC : 93.2 %

Example 79 : 1-Methyl-2,4-dioxo-3-[(E)-3-(pyridin-3-yl)-allyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-((E)-3-chloro-propenyl)-pyridine.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.63

NMR: DMSO ^1H δ (ppm) : 3.55 (s,3H); 3.75 (s,3H); 4.40 (d,2H); 4.75 (d,2H); 6.40-6.50 (m,1H); 6.50-6.60 (d,1H); 6.90 (d,2H); 7.20-7.35 (m,3H); 7.55 (d,1H); 7.85 (d,1H); 8.25 (d,1H); 8.40 (s,1H); 8.60 (d,2H); 9.20 (t,1H).

IR : 3395, 1703, 1643, 1509, 1479, 1254, 761 cm^{-1}

M.P. = 200.0 °C

HPLC : 98.7 %

Example 80 : 1-Methyl-2,4-dioxo-3-[(E)-3-(pyridin-4-yl)-allyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-((E)-3-chloro-propenyl)-pyridine.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.43

NMR: DMSO ^1H δ (ppm) : 3.55 (s,3H); 3.75 (s,3H); 4.45 (d,2H); 4.80 (d,2H); 6.55 (d,1H); 6.60-6.70 (m,1H); 6.90 (d,2H); 7.25 (d,2H); 7.35 (d,2H); 7.55 (d,1H); 8.25 (dd,1H); 8.45 (d,2H); 8.65 (s,1H); 9.20 (t,1H).

IR : 3395, 1704, 1643, 1509, 1479, 1332, 1254, 980, 765 cm^{-1}

M.P. = 241 °C

HPLC : 98.1 %

Example 81 : 1-Methyl-2,4-dioxo-3-(4-sulfamoyl-benzyl)-1,2,3,4-tetrahydro quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-bromomethyl-benzenesulfonamide.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.48

NMR: DMSO ^1H δ (ppm) : 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.30 (s,2H); 7.50 (d,2H); 7.55 (d,1H); 7.75 (d,2H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 3338, 1708, 1654, 1616, 1548, 1507, 1329, 1245, 1036, 825, 751 cm^{-1}

M.P. = 219.0 °C

HPLC : 94.9 %

Example 82 : 3-(4-Methanesulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the Step 1-5 to 2-5 of the preparation B using 3-(4-methanesulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid.

NMR: DMSO ^1H δ (ppm): 3.20 (s,3H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.15 (d,2H); 7.50-7.60 (m,3H); 7.85 (d,2H); 8.30 (dd,1H); 8.60 (s,1H); 9.20 (t,1H).

IR : 3370, 1707, 1658, 1641, 1303, 1148, 783 cm^{-1}

M.P. = 210°C

HPLC: 97.9 %

Example 83 : 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

Step 1 : Methyl 3-(4-chlorosulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate

Into a stirred round-bottomed flask protected from moisture, 3.2 ml (47.5 mmol) of chlorosulfonic acid are introduced. The mixture is cooled with an ice bath and 2.2 g (6.80 mmol) of compound obtained in the Step 1 of Preparation C are added slowly. After 3 hours stirring at room temperature, the reaction mixture is poured in an mixture of water and ice. The precipitate is filtered and dried to provide 1.8 g of the desired product.

NMR: DMSO ^{1}H δ (ppm) : 3.55 (s, 3H); 3.90 (s,3H); 5.15 (s,2H); 7.25 (m,2H); 7.50-7.60 (m,3H); 8.25 (dd,1H); .60 (s, 1H).

Step 2: Methyl 3-(4-dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate

To a stirred solution of 0.4 g (0.94 mmol) of the compound obtained in the preceding Step 1 in 25 ml of dichloromethane are added 3.3 ml (66 mmol) of dimethylamine 2M in THF. After 1 hour, the reaction mixture is concentrated under vacuum. A chromatography on silica gel (dichloromethane/acetone: 98/2) provides 0.370 g (yield : 91%) of the desired product.

NMR: DMSO ^{1}H δ (ppm): 2.6 (s,6H); 3.6 (s,3H); 3.9 (s,3H); 5.25 (d,2H); 7.60 (m,3H); 7.70 (m,2H); 8.25 (dd,1H); 8.60 (s,1H).

Step 3 : 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro quinazoline-6-carboxylic acid

The compound is obtained according to the procedure of the Step 2-4 of Preparation B, using as substrate the compound obtained in the preceding Step 2.

NMR: DMSO ^{1}H δ (ppm): 2.60 (s,6H); 3.55 (s,3H); 5.25 (s,2H); 7.60 (m,3H); 7.70 (m,2H); 8.25 (dd,1H); 8.60 (s,1H); 13.20 (bs,1H).

Step 4: 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Example 1, but using 4-methoxybenzylamine. The desired compound crystallizes in a mixture of dichloromethane/ether.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.48

NMR: DMSO ^{1}H δ (ppm) : 2.55 (s,6H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55-7.60 (m,3H); 7.60-7.70 (m,2H); 8.30 (d,1H); 8.65 (s,1H); 9.20 (t,1H).

IR : 1708, 1660, 1618, 1503, 1477, 1335, 1247, 1160, 952, 760, 718 cm^{-1}

M.P. = 112 °C

HPLC : 94.8 %

Example 84 : 3-[4-(2-Dimethylamino-ethylsulfamoyl)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according the procedure of Steps 1 to 4 of the Example 83 using *N,N'*-dimethylethylene diamine in the Step 2. The desired compound crystallizes in a mixture of dichloromethane/ether.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.47

NMR: DMSO ^{1}H δ (ppm) : 2.0-2.15 (m,6H); 2.20-2.35 (m,2H); 2.75-2.85 (m,2H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.85 (d,2H); 7.25 (d,2H); 7.45-7.65 (m,4H); 7.65-7.80 (m,2H); 8.25 (d,1H); 8.60 (m,1H); 9.20 (m,1H).

IR : 1707, 1656, 1618, 1508, 1477, 1326, 1249, 1155 cm^{-1}

M.P. = 114 °C

HPLC : 90.9 %

Example 85 : 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

Step 1 : Methyl 1-methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate

The compound is obtained according the procedure of Steps 1 to 3 of the Example 83 using methylamine in the Step 2.

Step 2 : 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

0.2 g (0,5 mmol) of the compound obtained in the preceding Step 1 is dissolved in 10 ml of dichloroethane. The solution is cooled and 3.2 ml (6.4 mmol) of trimethylaluminium 2M in toluene and 0.875 g (6.4 mmol) of 4-methoxy-benzylamine are added. The solution mixture is stirred overnight at room temperature and then 24 hours at 60°C. The solution is evaporated under vacuum and a chromatography over silica gel (dichloromethane/ether) provides 0.085 g (yield 32%) of the desired product.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.60

NMR: DMSO ^1H δ (ppm): 2.40 (d,3H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.85 (d,2H); 7.25 (d,2H); 7.40 (q,1H); 7.50 (d,2H); 7.60 (d,1H); 7.70 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H).

IR : 3338, 1708, 1654, 1616, 1548, 1507, 1329, 1245, 1036, 825, 751 cm^{-1}

M.P. = 217.0 °C

HPLC : 95.0 %

Example 86 : Methyl 3-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 3-(bromomethyl)benzoate.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.80

NMR: DMSO ^1H δ (ppm): 3.50 (s,3H); 3.70 (s,3H); 3.80 (s,3H); 4.40 (d,2H); 5.2 (s,2H); 6.80-6.90 (m,2H); 7.2- 7.3 (m,2H); 7.4-7.5 (m,1H); 7.5-7.6 (m,1H); 7.6-7.7 (m,1H); 7.8-7.9 (m,1H); 7.95 (s,1H); 8.30 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 3254, 1729, 1705, 1659, 1637, 1502, 1299, 1249, 749 cm^{-1}

M.P. = 193.5 °C

HPLC : 100 %

Example 87 : 3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using as substrate the compound of the Example 86.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.70

NMR: DMSO ^1H δ (ppm): 3.60 (s,3H); 3.70 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.40-7.45 (m,1H); 7.5-7.65 (m,2H); 7.80 (d,1H); 7.95 (s,1H); 8.20 (d,1H); 8.60 (s,1H); 9.2 (t,1H); 12.95 (s,1H)

IR : 3400, 3190, 1705, 1659, 1646, 1616, 1510, 1247, 1197, 750 cm^{-1}

M.P. = 182 °C

HPLC : 98.8 %

Example 88: (E) Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-but-2-enoate

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 4-bromocrotonate.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.75

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.60 (s,3H); 3.70 (s,3H); 4.45 (d,2H); 4.75 (d,2H); 5.9 (d,1H); 6.80-6.90 (m,2H); 6.9-6.95 (m,1H); 7.2-7.3 (m,2H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 3408, 1708, 1644, 1617, 1507, 1477, 1280, 1248, 1036, 765 cm^{-1}

M.P. = 107.9 °C

HPLC : 96.2 %

Example 89 : 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-but-2-enoic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using as substrate the compound of the Example 88.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.50

NMR: DMSO ^1H δ (ppm): 3.50 (s,3H); 3.70 (s,3H); 4.30 (d,2H); 4.70 (d,2H); 5.70-5.80 (m,1H); 6.70-6.85 (m,1H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.20-8.25 (m,1H); 8.60 (s,1H); 9.2 (t,1H); 12.3 (bs,1H)

IR : 3409, 1700, 1644, 1617, 1506, 1304, 1248, 767 cm^{-1}

M.P. = 245.5 °C

HPLC : 91.3 %

Example 90 : Methyl 5-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-furan-2-carboxylate

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 5-(chloromethyl)-2-furoate.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.60

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.70 (s,3H); 3.75 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.55 (d,1H); 6.85 (d,2H); 7.25 (m,3H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 3249,1711, 1664, 1636, 1503, 1446, 1299, 1250, 1148, 1023, 824, 765 cm^{-1}

M.P. = 195.5 °C

HPLC : 99.2 %

Example 91 : 5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-furan-2-carboxylic acid

The compound is obtained by hydrolysis, in the presence of K_2CO_3 in a mixture of dioxane/water, of the compound of the Example 90.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.10

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.40 (s,2H); 5.20 (s,2H);6.50 (s,1H); 6.90 (d,2H); 7.10 (s,1H); 7.25 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H); 13.05 (bs,1H).

IR : 1711, 1661, 1618, 1505, 1477, 1326, 1248, 1141, 1024, 968, 824, 787 cm^{-1}

M.P. = 198 °C

HPLC : 100.0 %

Example 92: Methyl 5-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-thiophene-2-carboxylate

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 5-bromomethyl-thiophene-2-carboxylate. This compound is obtained according to the procedure described in *J. Med. Chem.*, 1998, 41 (1), 74-95.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.20

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.75 (s,3H); 3.80 (s,3H); 4.40 (d,2H); 5.30 (s,2H); 6.90 (d,2H); 7.15 (d,1H); 7.25 (d,2H); 7.55 (d,1H); 7.60 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 3249, 1707, 1660, 1635, 1515, 1326, 1294, 1092, 1036, 625, 749 cm^{-1}

M.P. = 200.5°C

HPLC : 91.5 %

Example 93 : 5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-thiophene-2-carboxylic acid

The compound is obtained by hydrolysis, in the presence of K_2CO_3 in a mixture of dioxane/water, of the compound of the Example 92.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.25

NMR: DMSO ^1H δ (ppm) : 3.55 (s,3H); 3.70 (,3H); 4.40 (d,2H); 5.30 (s,2H); 6.90 (d,2H); 7.15 (d,1H); 7.25 (d,2H); 7.55 (m,2H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H); 13.0 (m,1H).

IR : 3241, 1705, 1662, 1632, 1541, 1325, 1246, 1032, 921, 826, 783 cm^{-1}

M.P. = 198.5 °C

HPLC : 92.2 %

Example 94 : 1-Methyl-3-(4-nitro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-nitrobenzyl bromide.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.47

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50-7.65 (m,3H); 8.15 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H).

IR : 1706,1661, 1618, 1513, 1477, 1345, 1248, 752 cm^{-1}

M.P. = 129.0 °C

HPLC : 100 %

Example 95 : 3-(4-Amino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

1 g (2.1 mmol) of the compound of Example 94 is hydrogenated with Pd/C in a mixture of dichloromethane/methanol 80/20 v/v. After 2 hours of stirring under hydrogen atmosphere, the reaction mixture is filtered. The solvent is removed under vacuum and the crude product is concretized from a mixture of dichloromethane/ether to provide 0.800 g of the desired compound (yield: 85.8%).

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.19

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.45 (d,2H); 4.90-5.05 (m,4H); 6.45 (d,2H); 6.90 (d,2H); 7.05 (d,2H); 7.25 (d,2H); 7.50 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 3387, 1701, 1647, 1615, 1511, 1478, 1245, 789 cm^{-1}

M.P. = 167 °C

HPLC : 99.0 %

Example 96 : 3-(4-Dimethylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

To a round bottom flask protected from the moisture are added successively 0.220 g (0.5 mmol) of the compound of Example 95 in 5 ml of CH_3CN, and under stirring 0.150 g (5

mmol) of powder of paraformaldehyd, 0.095 g (1.5 mmol) of $NaBH_3CN$ and 100 µl of acetic acid. After 2 hours at room temperature and 1h30 under reflux, the reaction mixture is taken up in dichloromethane and washed with a solution of NaOH 1M. The organic phase is decanted, washed, dried and then concentrated under vacuum. The product is recrystallized from acetonitrile to provide 0.130 g (yield : 55%) of the desired compound.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.42

NMR: DMSO ^1H δ (ppm): 2.80 (s,6H); 3.50 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.00 (s,2H); 6.60 (d,2H); 6.90 (d,2H); 7.15-7.25 (m,4H); 7.50 (d,1H); 8.20 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 1699, 1654, 1640, 1616, 1508, 1324, 1324 cm^{-1}

M.P. = 205.0°C

HPLC : 98.9 %

Example 97 : 3-(4-Acetylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

To a round bottom protected from the moisture is added 0.190 g (0.43 mmol) of the compound of Example 95 in 10 ml of dichloromethane. The solution is stirred and 36 µl (40 mg, 0.51 mmol) of acetyl chloride and 72 µl of triethylamine are added. After 1 hour at room temperature 36 µl of acetyl chloride and 72 µl of triethylamine are added. After 1 hour, the organic phase is washed with a solution of HCl 1M and dried. A chromatography over silica gel (dichloromethane/ether) provides 0.120 g (yield: 57%) of the desired product.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.17

NMR: DMSO ^1H δ (ppm) : 2.0 (s,3H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.05 (s,2H); 6.90 (d,2H); 7.20-7.30 (m,4H); 7.45 (d,2H); 7.50 (d,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H); 9.85 (s,1H).

IR : 3330, 1661, 1617, 1511, 1475, 1322, 1244, 825, 752 cm^{-1}

M.P. = 251.0 °C

HPLC : 100.0 %

Example 98 : 3-[4-(N,N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Example 97 using as substrates the compound obtained in the Example 95 and methanesulfonyl chloride.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.40

NMR: DMSO ^1H δ (ppm): 3.50 (s,6H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.40-7.50 (m,4H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H).

IR : 1655, 1639, 1507, 1376, 1252, 1157, 905, 761 cm^{-1}

M.P. = 198 °C

HPLC : 100.0 %

Example 99 : 3-(Benzofurazan-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 5-bromomethyl benzofurazan.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.80

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.60 (m,2H); 7.90 (s,1H); 8.0 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H).

IR : 2370, 1701, 1653, 1617, 1499, 1477, 1326, 1243, 1181, 1028, 881, 781 cm^{-1}

M.P. = 140.5°C

HPLC : 100.0 %

Example 100 :3-[2-(4-Fluorophenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 4-fluorophenoxyethyl bromide.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.60

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.20 (d,2H); 4.3-4.4 (m,2H); 4.4-4.50 (m,2H); 6.80-7.0 (m,4H); 7.0-7.1 (m,2H); 7.2-7.30 (m,2H); 7.4-7.5 (m,1H); 8.20-8.30 (m,1H); 8.60-8.70 (m,1H); 9.2 (t,1H).

IR : 1707, 1656, 1641, 1520, 1475, 1247, 1209, 1034, 828, 752 cm^{-1}

M.P. = 159.6 °C

HPLC : 99.7 %

Example 101 :3-(2-Benzenesulfonyl-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 2-chloroethyl phenyl sulphone.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.55

NMR: DMSO ^1H δ (ppm): 3.50 (s,3H); 3.6-3.70 (m,2H); 3.75 (s,3H); 4.3 (d,2H); 4.4-4.50 (m,2H); 6.90 (d,2H); 7.30 (d,2H); 7.4-7.7 (m,4H); 7.9 (d,2H); 8.20 (d,1H); 8.60 (s,1H); 9.2 (t,1H).

IR : 3274, 1708, 1663, 1638, 1514, 1499, 1249, 1147, 1034, 825, 746 cm^{-1}

M.P. = 192.9°C

HPLC : 96.0 %

Example 102 :3-(3-fluoro-4-methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy benzylamine

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 4-chloromethyl-2-fluoro-1-methoxy-benzene.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.80

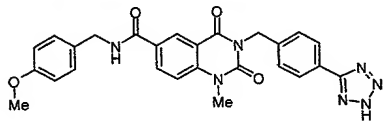
NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.75 (s,3H); 3.80 (s,3H); 4.4 (d,2H); 5.10 (s,2H); 6.90 (d,2H); 7.20 (m,5H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.2 (t,1H).

IR : 3411, 2362, 1705, 1644, 1617, 1513, 1325, 1275, 1246, 1028, 827, 786 cm^{-1}

M.P. = 136 °C

HPLC : 100.0 %

Example 103: 1-Methyl-2,4-dioxo-3-[4-(2H-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide



A solution of 3 g (6.6 mmol) of compound of the Example 60 in 100 ml of toluene, 1.3 g (19.8 mmol) of NaN_3 and 2.72 g (19.8 mmol) of triethylamine hydrochloride are heated at 80°C under an inert atmosphere. After 5 hours, 10 ml of DMF are added and the reflux is maintained overnight. After cooling, the precipitate is filtered and washed successively with AcOEt, MeOH and HCl 3N. The solid obtained is treated under reflux by a mixture of AcOEt/MeOH and filtered. A chromatography over silica gel (DMF with NH_4OH 10%) provides 1.2 g of the desired compound (yield : 36%).

TLC : CH_2Cl_2 / MeOH 80/20 Rf = 0.30

NMR: DMSO ^1H δ (ppm): 3.50 (bs,1H);.3.55 (s,3H); 3.70 (s,3H); 4.4 (m,2H); 5.20 (s,2H); 6.90 (m,2H); 7.25 (m,2H); 7.50 (m,3H); 8.0 (m,2H); 8.3 (m,1H); 8.70 (s,1H); 9.2 (m,1H).

M.P. = 286°C

HPLC : 96.7 %

Example 104 :1-Methyl-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 3-(4-chloromethyl-phenyl)-5-methyl-[1,2,4]oxadiazole (which is obtained in 4 steps from 4-hydroxymethyl-benzonitrile).

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.50

NMR: $CDCl_3$ ^1H δ (ppm): 2.60 (s,3H); 3.60 (s,3H); 3.80 (s,3H); 4.55 (m,2H); 5.25 (s,2H); 6.60 (s,1H); 6.85 (m,2H); 7.30 (m,3H); 7.55 (m,2H); 7.90 (m,2H); 8.3 (m,1H); 8.50 (s,1H).

M.P. = 235.0°C

HPLC : 95.1 %

Example 105 :1-Methyl-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

To a round bottom containing 4Å molecular sieves, 5 ml of DMF, 76 mg (1.02 mmol) of *N*-hydroxy-acetamidine and 25 mg (1.02 mmol) of NaH are introduced. The mixture is stirred for 15 minutes and 0.5 g (1.02 mmol) of compound of the Example 34 is added. The reaction is heated at 65°C for 4 hours and then filtered over Celite. The filtrate is poured onto 100 ml of water. The precipitate obtained is filtered, washed successively by ethanol, water and ether, and dried to provide 0.210 g (yield: 40%) of the desired compound.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.50

NMR: DMSO ^1H δ (ppm): 3.3 (s,3H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (m,2H); 5.25 (s,2H); 6.90 (m,2H); 7.25 (m,2H); 7.55 (m,3H); 8.0 (d,2H); 8.3 (m,1H); 8.60 (s,1H); 9.2 (m,1H).

M.P. = 226.0°C

HPLC : 98.6 %

Example 106 :Methyl 2-chloro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and methyl 2-chloro-4-chloromethyl-benzoate.

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.70 (s,3H); 3.80 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.90 (m,2H); 7.25 (m,3H); 7.60 (d,1H); 7.75 (d,1H); 7.95 (s,1H); 8.3 (m,1H); 8.70 (s,1H); 9.2 (m,1H).

M.P. = 229.0°C

HPLC: 98.8 %

Example 107 :2-Chloro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

The compound is obtained by hydrolysis of the compound of Example 106 with a solution of aqueous methanol and K_2CO_3.

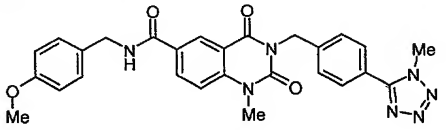
TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.30

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.40 (m,2H); 5.20 (s,2H); 6.85 (m,2H); 7.20 (m,3H); 7.60 (m,1H); 7.70 (m,1H); 7.95 (m,1H); 8.3 (m,1H); 8.60 (s,1H); 9.2 (m,1H); 13.2 (s,1H).

M.P. = 216.0°C

HPLC: 96.5 %

Example 108 :1-Methyl-3-[4-(1-methyl-1*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide



The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 5-(4-chloromethyl-phenyl)-1-methyl-1*H*-tetrazole

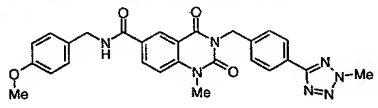
TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.40

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.70 (s,3H); 4.10 (s,3H); 4.40 (m,2H); 5.20 (s,2H); 6.80 (d,2H); 7.25 (d,2H); 7.50 (m,3H); 7.80 (m,2H); 8.2 (d,1H); 8.60 (s,1H); 9.2 (s,1H).

M.P. = 143.0°C

HPLC : 100 %

Example 109 :1-Methyl-3-[4-(2-methyl-2*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide



The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 5-(4-chloromethyl-phenyl)-2-methyl-2*H*-tetrazole.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.50

NMR: DMSO ^1H δ (ppm): 3.50 (s,3H); 3.70 (s,3H); 4.40 (m,5H); 5.20 (s,2H); 6.90 (m,2H); 7.25 (m,2H); 7.50 (m,3H); 8.0 (m,2H); 8.3 (d,1H); 8.60 (s,1H); 9.2 (m,1H).

M.P. = 226.0°C

HPLC : 98.2 %

Example 110 :Methyl 2-methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and methyl 4-bromomethyl-2-methoxy-benzoate.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.60

NMR: $CDCl_3$ ^1H δ (ppm): 3.60 (s,3H); 3.80 (s,3H); 3.85 (s,3H); 3.90 (s,3H); 4.55 (d,2H); 5.20 (s,2H); 6.45 (m,1H); 6.80 (d,2H); 7.05 (d,1H); 7.20 (m,4H); 7.70 (d,1H); 8.3 (d,1H); 8.50 (s,1H).

M.P. = 170.0°C

HPLC : 98.6 %

Example 111 :2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

The compound is obtained by hydrolysis of compound of the Example 110 using as reagent K_2CO_3 in a mixture of methanol and water. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.50

NMR: DMSO ^1H δ (ppm): 3.60 (s,3H); 3.70 (s,3H); 3.80 (s,3H); 4.40 (s,2H); 5.15 (s,2H); 6.90 (m,3H); 7.10 (s,1H); 7.30 (m,2H); 7.60 (m,2H); 8.3 (m,1H); 8.60 (s,1H); 9.2 (m,1H); 12.5 (bs,1H).

M.P. = 189°C

HPLC: 100.0 %

Example 112 :Methyl 2-hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

To a stirred solution of 1 g (1.93 mmol) of compound of the Example 111 in 15 ml of dichloromethane, maintained at 0°C, are added dropwise, under an inert atmosphere, 7.7 ml (7.7 mmol) of BCl_3 1M/l in dichloromethane. After 15 minutes of stirring at 0°C and 1 hour at room temperature, the reaction mixture is poured on ice and extracted by ethyl acetate. The organic phase is dried and concentrated under vacuum. The precipitate obtained is purified by chromatography over silica gel (dichloromethane/methanol: 99/1) to provide 0.460 g (yield : 47%) of the desired product.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.60

NMR: DMSO ^1H δ (ppm): 3.50 (s,3H); 3.70 (s,3H); 3.85 (s,3H); 4.40 (d,2H); 5.10 (s,2H); 6.85 (m,4H); 7.25 (d,2H); 7.55 (d,1H); 7.70 (d,1H); 8.3 (m,1H); 8.60 (s,1H); 9.2 (m,1H); 10.5 (s,1H).

M.P. = 205.0 °C

HPLC : 100.0 %

Example 113 :2-Hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

The compound is obtained by hydrolysis of compound of the Example 112 using as reagent K_2CO_3 in a mixture of methanol and water. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.60

NMR: DMSO ^1H δ (ppm): 3.50 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.15 (s,2H); 6.80 (m,4H); 7.25 (m,2H); 7.55 (m,1H); 7.70 (d,1H); 8.3 (m,1H); 8.60 (s,1H); 9.2 (m,1H); 11.3 (bs,1H); 13.8 (s,1H).

M.P. = 262.0 °C

HPLC : 98.2 %

Example 114 :Methyl 2-methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and methyl 4-bromomethyl-2-methyl benzoate.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.80

NMR: DMSO ^1H δ (ppm): 2.5 (s,3H); 3.50 (s,3H); 3.70 (s,3H); 3.80 (s,3H); 4.40 (s,2H); 5.10 (s,2H); 6.90 (m,2H); 7.25 (m,4H); 7.50 (d,1H); 7.70 (d,1H); 8.2 (m,1H); 8.60 (s,1H); 9.2 (s,1H).

M.P. = 167.0°C

HPLC : 100.0 %

Example 115 :2-Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

The compound is obtained by hydrolysis of compound of the Example 114 using first as reagent K_2CO_3 in a mixture of methanol and water, and secondly LiOH in reflux for 2 days. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired compound.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.50

NMR: DMSO ^1H δ (ppm): 2.5 (s,3H); 3.55 (s,3H); 3.80 (s,3H); 4.40 (d,2H); 5.10 (s,2H); 6.80 (d,2H); 7.25-7.1 (m,4H); 7.55 (m,1H);7.75 (m,1H); 8.2 (d,1H); 8.60 (s,1H); 9.2 (t,1H); 12.7 (s,1H)

M.P. = 179.0 °C

HPLC : 95.6 %

Example 116 :1-Methyl-2,4-dioxo-3-(pyridin-4-methyl)-1,2,3,4-tetrahydro-quinazoline-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide

Step 1 : Methyl 2,4-dioxo-1-methyl-3-(pyridine-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylate

The compound is obtained according to the procedure of the Step 4 of Example 15 using the compound obtained in the Step 2 of the Example 20.

Step 2: 2,4-Dioxo-1-methyl-3-(pyridine-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the preceding Step 1.

Step 3: 1-Methyl-2,4-dioxo-3-(pyridin-4-methyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide

To a stirred solution of 0.2 g (0.65 mmol) of compound obtained in the preceding Step 2 in 7 ml of dichloromethane are added 0.113 g (0.65 mmol) of EDCI, 0.080 g (0.65 mmol) of HOBT and 0.064 g (0.060 ml, 0.65 mmol) of 3,4-methylenedioxy-benzylamine. After 20 hours of stirring at room temperature and an usual treatment, 0.140 g (yield: 48%) of the desired product are obtained.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.80

NMR: DMSO ^1H δ (ppm): 3.60 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.0 (s,2H); 6.80-6.95 (m,3H); 7.25-7.35 (m,2H); 7.55-7.60 (m,1H); 8.25-8.35 (m,1H); 8.45-8.50 (m,2H); 8.65 (s,1H); 9.20 (t,1H).

IR : 3265, 1707, 1663, 1618, 1501, 1490, 1254, 1037, 925 cm^{-1}

M.P. = 161.7°C

HPLC : 94.6 %

Example 117 :1-Methyl-2,4-dioxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 3 of Example 116 using the compound obtained in the Step 2 of the Example 116 and 4-methoxy-benzylamine. 0.280 g (yield : 25%) of the desired product is isolated after a chromatography over silica gel.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.70

NMR: DMSO ^1H δ (ppm): 3.60 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.15 (s,2H); 6.80 (d,2H); 7.2-7.3 (m,4H); 7.55-7.60 (m,1H); 8.25-8.30 (m,1H); 8.45 (d,2H); 8.60 (s,1H); 9.20 (m,1H).

IR : 3231, 1706, 1657, 1625, 1505, 1324, 1248, 1039, 827 cm^{-1}

M.P. = 180.7 °C

HPLC : 94.3 %

Example 118 :1-Methyl-2,4-dioxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-hydroxy-benzylamide

To a stirred solution of 0.280 g (0.67 mmol) of compound of the Example 117 in 20 ml of dichloromethane, maintained at 0°C, are added, under an inert atmosphere, 1.7 g (0.63 ml, 6.7 mmol) of BBr_3 in 2 ml of dichloromethane. After 20 minutes of stirring at room temperature, the reaction mixture is poured on a saturated solution of $NaHCO_3$, decanted, and extracted. The organic phase is dried and concentrated under vacuum to provide 0.150 g (yield : 53.4%) of the desired product.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.60

NMR: DMSO ^1H δ (ppm): 3.60 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.70 (d,2H); 7.15 (d,2H); 7.3 (d,2H); 7.55-7.60 (m,1H); 8.30 (d,1H); 8.50 (d,2H); 8.65 (s,1H); 9.20 (m,1H); 9.30 (s,1H)

IR : 3388, 1701, 1656, 1639, 1615, 1508, 1251, 830, 772, 751 cm^{-1}

M.P. = 137.7°C

HPLC : 91.1 %

Example 119 :Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

Step 1 : Benzyl 3-(4-methoxycarbonyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline -6-carboxylate

The compound is obtained according to the procedure of Step 1-5 to Step 2-5 of the Preparation B using, in Step 1-5, 4-amino-isophtalic acid 1-benzylester 3-methyl ester and methyl 4-aminomethyl benzoate. The desired product is purified by reflux in methanol.

TC : CH_2Cl_2 / MeOH 95/5 Rf = 0.65

NMR: DMSO ^1H δ (ppm): 3.8 (s, 3H); 5.10 (s,2H); 5.35 (s,2H); 7.20-7.80 (m,8H); 7.80-7.90 (m,2H); 8.20-8.30 (m,1H); 8.50 (s,1H); 11.90 (s,1H).

HPLC : 97.0 %

Step 2 : Benzyl 3-(4-methoxycarbonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate

The compound is obtained according to the procedure of the Step 4 of the Example 15 using the compound obtained in the preceding Step 1.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.65

NMR: DMSO ^1H δ (ppm): 3.60 (s,3H); 3.80 (s,3H); 5.20 (s,2H); 5.35 (s,2H); 7.30-7.60 (m,8H); 7.80-7.90 (m,2H); 8.20-8.30 (m,1H); 8.60 (s,1H).

HPLC : 97.0 %

Step 3 : 3-(4-Methoxycarbonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid

To a stirred solution of 10.8 g (23.6 mmol) of the compound obtained in the preceding Step 2 in 120 ml of dichloromethane and 80 ml of methanol, are added 3.2 g of Pd/C at 10%. The reaction mixture is stirred under hydrogen atmosphere for 1 hour at room temperature, followed by filtration over Celite. The filtrate is concentrated under vacuum to give a first crystallized crop. The unsoluble part is extracted three times by a mixture of methanol/water/saturated solution of $NaHCO_3$. The organic phases are gathered and acidified to pH 1 by a concentrated solution of chlorhydric acid, to give to a second crop corresponding to the desired product. The two crops are put together and dried under vacuum to provide 6.9 g of the desired product (yield : 79%).

NMR: DMSO ^1H δ (ppm): 3.60 (s,3H); 3.80 (s,3H); 5.20 (s,2H); 7.40 (dd,2H); 7.60 (dd,1H); 7.90 (dd,2H); 8.30 (dd,1H); 8.60 (s,1H); 13.20 (bs,1H).

HPLC : > 97.0 %

Step 4 : Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 3 and 3-methoxy-benzylamine.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.70

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.70 (s,3H); 3.80 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 6.80 (d,1H); 6.90 (m,2H); 7.25 (m,1H); 7.45 (d,2H); 7.55 (d,1H); 7.85 (d,2H); 8.25 (d,1H); 8.60 (s,1H); 9.25 (t,1H).

IR : 3435, 2361, 1716, 1703, 1666, 1617, 1498, 1455, 1282, 1125, 839, 749, cm^{-1}

M.P. = 199.0°C

HPLC : 98.6 %

Example 120 :4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

The compound is obtained by hydrolysis of compound of the Example 119 using as reagent K_2CO_3 in a mixture of methanol and water under reflux for 8 hours. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.40

NMR: DMSO ^1H δ (ppm) : 3.55 (s,3H); 3.75 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 6.80 (d,1H); 6.90 (m,2H); 7.25 (t,1H); 7.45 (d,2H); 7.55 (d,1H); 7.85 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.25 (t,1H); 12.85 (bs,1H)

IR : 3395, 2345, 1719, 1647, 1616, 1501, 1310, 1238, 1052, 839, 781, 751 cm^{-1}

M.P. = 279.0°C

HPLC : 97.4 %

Example 121 :Methyl 4-[1-methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the Step 3 of Example 119 and 4-methylthio-benzylamine.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.80

NMR: DMSO ^1H δ (ppm) : 2.45 (s,3H); 3.55 (s,3H); 3.80 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 7.20 (m,4H); 7.45 (d,2H); 7.55 (s,1H); 7.90 (d,2H); 8.25 (d,1H); 8.60 (s,1H); 9.20 (t,1H).

IR : 3395, 1708, 1656, 1641, 1508, 1479, 1330, 1280, 1254, 1117, 783, 749, cm^{-1}

M.P. = 172 °C

HPLC : 99.2 %

Example 122 :4-[1-Methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

The compound is obtained by hydrolysis of compound of the Example 121 using as reagent K_2CO_3 in a mixture of methanol and water under reflux for 48 hours. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.35

NMR: DMSO ^1H δ (ppm): 2.45 (s,3H); 3.55 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 7.25 (m,4H); 7.40 (d,2H); 7.55 (d,1H); 7.85 (d,2H); 8.25 (d,1H); 8.60 (s,1H); 9.25 (t,1H); 12.85 (bs,1H);

IR : 1705, 1656, 1642, 1616, 1479, 1330, 1247, 1101, 1020, 760, 751 cm^{-1}

M.P. = 171 °C

HPLC : 98.0 %

Example 123 :Methyl 4-[1-methyl-2,4-dioxo-6-(4-trifluoromethoxy-benzylcarbamoyl)-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the Step 3 of Example 119 and 4-trifluoromethoxy-benzylamine.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.35

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.80 (s,3H); 4.50 (d,2H); 5.20 (s,2H); 7.30 (d,2H); 7.35-7.50 (m,4H); 7.55 (d,1H); 7.90 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.30 (t,1H).

IR : 1712, 1656, 1639, 1506, 1274, 1156, 1104, 751 cm^{-1}

M.P. = 212 °C

HPLC : 99.6 %

Example 124 :Methyl 4-[6-(4-fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 3 and 4-fluorobenzylamine.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.45

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.80 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 7.10-7.20 (m,2H); 7.30-7.40 (m,2H); 7.40-7.50 (d,2H); 7.55 (d,1H); 7.85 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.25 (t,1H).

IR : 1709, 1657, 1618, 1499, 1264, 768, 749, 716 cm^{-1}

M.P. = 198 °C

HPLC : 98.2 %

Example 125 :4-[6-(4-Fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the Example 124.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.25

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 4.45 (d,2H); 5.20 (s,2H); 7.10-7.20 (m,2H); 7.30-7.40 (m,2H); 7.45 (d,2H); 7.55 (d,1H); 7.90 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.25 (t,1H); 12.90 (bs,1H)

IR : 3661, 2765, 1710, 1649, 1617, 1505, 1224, 829, 752 cm^{-1}

M.P. = 272 °C

HPLC : 98.0 %

Example 126 :Methyl 4-{6-[(benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the Step 3 of Example 119 and *C*-benzofurazan-5-yl-methylamine, which is obtained from 5-bromomethyl-benzofurazan by reaction in a first step with sodium diformylamide in acetonitrile at 70°C overnight, and in a second step by a treatment for 2 hours under reflux to a solution of ethanol/HCl 5%.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.70

NMR: DMSO ^{1}H δ (ppm): 3.55 (s,3H); 3.85 (s,3H); 4.65 (d,2H); 5.25 (s,2H); 7.45 (d,2H); 7.60 (d,2H); 7.90 (m,3H); 8.00 (d,1H); 8.30 (d,1H); 8.65 (s,1H); 9.40 (t,1H).

IR : 3257, 1731, 1702, 1659, 1619, 1506, 1419, 1281, 1109, 877, 769, 751 cm^{-1}

M.P. = 234 °C

HPLC : 98.6 %

Example 127: 4-{6-[(Benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the Example 126. After acidification, the precipitate is filtered off.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.35

NMR: DMSO ^{1}H δ (ppm): 3.55 (s,3H); 4.60 (d,2H); 5.20 (s,2H); 7.40 (d,2H); 7.60 (d,2H); 7.85 (d,3H); 8.00 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.40 (t,1H); 12.9 (bs,1H).

IR : 3249, 1708, 1662, 1617, 1479, 1427, 1322, 1250, 1008, 879, 790, 754 cm^{-1}

M.P. = 276 °C

HPLC : 97.6 %

Example 128 :Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

Step 1 : 4-Amino-isophtalic acid 3-methyl ester

The compound is obtained according to the procedure of the Step 3of the Example 119 using as substrate 4-amino-isophtalic acid 1-benzylester 3-methyl ester.

Step 2: 6-Amino-*N*-(4-methoxy-benzyl)-isophtalamic acid methyl ester

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 1 and 4-methoxy-benzylamine.

Step 3 : Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-

quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 1-5 to 2-5 of the Preparation B using in the Step 1-5 the compound obtained in the preceding Step 2 and methyl 4-aminomethyl benzoate.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.55

NMR: DMSO ^1H δ (ppm): 3.70 (s,3H); 3.80 (s,3H); 4.40 (d,2H); 5.15 (s,2H); 6.90 (d,2H); 7.20 (m,3H); 7.45 (d,2H); 7.90 (d,2H); 8.15 (d,1H); 8.50 (s,1H); 9.15 (t,1H); 11.8 (s,1H).

IR : 3265, 2935, 2553, 1719, 1665, 1637, 1514, 1459, 1275, 1105, 827, 751 cm^{-1}

M.P. = 287.5 °C

HPLC : 98.3 %

Example 129 :Methyl 4-[1-ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 4 of the Example 15 using the compound obtained the Example 128 and iodomethane in DMF with K_2CO_3. The desired compound crystallizes in a mixture of dichloromethane/ether.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.55

NMR: DMSO ^1H δ (ppm): 1.25 (t,3H); 3.75 (s,3H); 3.85 (s,3H); 4.20 (d,2H); 4.40 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.45 (d,2H); 7.60 (d,1H); 7.90 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H).

IR : 3403, 2361, 1708, 1659, 1646, 1615, 1508, 1273, 1251, 1113, 847, 758 cm^{-1}

M.P. = 190 °C

HPLC : 96.9 %

Example 130 :4-[1-Ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

The compound is obtained by hydrolysis of compound of the Example 112 using as reagent K_2CO_3 in a mixture of methanol and water under reflux for 3 hours. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.45

NMR: DMSO ^1H δ (ppm): 1.25 (t,3H); 3.70 (s,3H); 4.20 (q,2H); 4.40 (d,2H); 5.20 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.40 (d,2H); 7.60 (d,1H); 7.85 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H); 12.85 (bs,1H)

IR : 2361, 1708, 1655, 1616, 1501, 1466, 1322, 1250, 1177, 1032, 823, 754 cm^{-1}

M.P. = 160 °C

HPLC : 98.2 %

Example 131 :3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

Step 1 : Methyl 3-(4-methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate

The compound is obtained according to the procedure of the Step 4 of the Example 15 using the compound obtained in the Step 1 of example 16.

Step 2: 3-(4-methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the preceding Step 1.

Step 3: 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

The compound is obtained (0.160 g, yield : 63%) according to the procedure of the Step 3 of the Example 116 using the compound obtained in the preceding Step 2 and 4-(aminomethyl)pyridine.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.70

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.7 (s,3H); 4.5 (d,2H); 5.10 (s,2H); 6.80-6.90 (m,2H); 7.30-7.35 (m,4H); 7.55-7.60 (m,1H); 8.25-8.30 (m,1H); 8.38-8.42 (m,2H); 8.70 (s,1H); 9.35 (t,1H).

IR : 3269, 1705, 1659, 1644, 1615, 1510, 1245, 1180, 842, 785 cm^{-1}

M.P. = 213.9 °C

HPLC : 97.8 %

Exemple 132 : 3-(4-Hydroxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

To a stirred solution of 0.630 g (1.46 mmol) of compound of the Example 131 in 50 ml of dichloromethane are added, under an inert atmosphere, 3.7 g (1.3 ml, 14.6 mmol) of BBr_3 in 5 ml of dichloromethane. After 1 hour of stirring at room temperature, the reaction mixture is cooled and poured on 100 ml of a saturated solution of $NaHCO_3$. The precipitate obtained is purified by chromatography over silica gel (gradient of methanol in dichloromethane) and solidified in dichloromethane to provide the desired compound.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.50

NMR: DMSO ^1H δ (ppm): 3.45 (s,3H); 4.45 (d,2H); 5.0 (s,2H); 6.60 (d,2H); 7.1 (d,2H); 7.25 (d,2H); 7.5 (d,1H); 8.20 (d,1H); 8.40 (d,2H); 8.60 (s,1H); 9.20 (s,1H); 9.20 (t,1H).

IR : 3048, 1705, 1659, 1642, 1507, 1479, 1328, 1244, 831 cm^{-1}

M.P. = 262.0 °C

HPLC : 94.8 %

Example 133: 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

The compound is obtained according to the procedure of the Example 33 using the same substrate and 4-picolylamine in the step of amidification.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.25

NMR: DMSO ^1H δ (ppm): 3.45 (s,3H); 4.5 (d,2H); 7.3 (d,2H); 7.55 (d,1H); 8.25 (d,1H); 8.5 (d,2H); 8.6 (s,1H); 9.35 (t,1H); 11.7 (s,1H).

IR : 3185,1686,1618,1479,1417,1326,782 cm^{-1}

M.P. = 292 °C

HPLC : 96.4 %

Step 2: 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the preceding Step 1 and α-bromo-*para*-toluonitrile.

TLC : AcOEt Rf = 0.55

NMR:.$CDCl_3$ ^1H δ (ppm): 3.60 (s,3H); 4.60 (d,2H); 5.30 (s,2H); 7.3 (m,3H); 7.60 (s,4H); 8.40 (m,1H); 8.45 (m,2H); 8.65 (m,1H); 8.80 (s,1H).

M.P. = 258°C

HPLC : 98.9 %

Example 134 :1-Methyl-2,4-dioxo-3-(3-pyridin-4-yl-allyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of Example 133 and 4-(3-chloro-propenyl)-pyridine hydrochloride.

TLC :CH_2Cl_2 / MeOH 90/10 Rf = 0.50

NMR: DMSO ^1H δ (ppm): 3.60 (s,3H); 4.50 (m,2H); 4.80 (m,2H); 6.50 (m,1H); 6.65 (m,1H); 7.3 (m,2H); 7.40 (m,2H); 7.60 (d,1H); 8.25 (d,1H); 8.50 (m,4H); 8.65 (s,1H); 9.35 (m,1H).

M.P. = 117°C

HPLC : 99.5 %

Example 135 :Methyl 4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of Example 133 and methyl-4-(bromomethyl)-benzoate.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.45

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 3.80 (s,3H); 4.5 (d,2H); 5.20 (s,2H); 7.3 (m,2H); 7.45 (d,2H); 7.60 (d,1H); 7.90 (m,2H); 8.25 (d,1H); 8.5 (m,2H); 8.65 (s,1H); 9.35 (t,1H).

IR : 3265, 1718, 1704, 1663, 1641, 1318, 1289, 1113, 751 cm^{-1}

M.P. = 236 °C

HPLC : 97.5 %

Example 136 :4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the Example 135. The corresponding hydrochloride is obtained after dissolution of the compound in a hot solution of isopropanol/ HCl 0.1 M. The desired compound is purified by crystallization from acetonitrile.

NMR: DMSO ^1H δ (ppm): 2.4-4.40 (m,1H); 3.60 (s,3H); 4.15 (t,2H); 5.20 (s,2H); 7.40 (d,2H); 7.60 (d,1H); 7.90 (m,4H); 8.30 (d,1H); 8.70 (s,1H); 8.80 (d,1H); 9.65 (t,1H); 12.9 (bs,1H).

IR : 3265, 1718, 1704, 1663, 1641, 1318, 1289, 1113, 751 cm^{-1}

M.P. = 268 °C

HPLC : 97.9 %

Example 137 :Methyl (4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-phenyl)-acetate

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of Example 133 and methyl 4-(bromomethyl-phenyl) acetate.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.45

NMR: DMSO ^1H δ (ppm): 3.50-3.60 (s,6H); 3.65 (s,2H); 4.5 (t,2H); 5.15 (s,2H); 7.20 (m,2H); 7.20-7.35 (m,4H); 7.55 (d,1H); 8.25 (d,1H); 8.5 (d,2H); 8.65 (s,1H); 9.35 (t,1H).

IR : 3298, 1736, 1707, 1663, 1631, 1505, 1473, 1320, 1157, 751 cm^{-1}

M.P. = 141 °C

HPLC : 96.4 %

Example 138 :(4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-phenyl)-acetic acid

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the Example 137. The corresponding hydrochloride is obtained after dissolution of the compound in a hot solution of isopropanol/ HCl 0.1 M. The desired compound is purified by crystallization from acetonitrile.

NMR: DMSO ^{1}H δ (ppm): 2.50-5.50 (bs,HCl+OH); 3.45-3.60 (2s,5H); 4.70 (d,2H); 5.15 (s,2H); 7.15 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 7.85 (d,2H); 8.30 (d,1H); 8.65 (s,1H); 8.75 (d,2H); 9.55 (t,1H).

IR : 3298, 1736, 1707, 1663, 1631, 1505, 1473, 1320, 1157, 751 cm^{-1}

M.P. = 241 °C

HPLC : 97.5 %

Example 139 :Methyl 4-{1-methyl-2,4-dioxo-6-[(1-oxy-pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate

To a stirred suspension of 0.500 g (1.10 mmol) of compound of the Example 135 in 20 ml of dichloromethane, maintained at -20°C, are added 0.250 g (1.10 mmol) of *meta*-chloroperbenzoic acid in 5 ml of dichloromethane. After stirring overnight at room temperature, the reaction mixture is washed successively with a saturated solution of Na_2CO_3 and water. The organic phase is dried and concentrated under vacuum. A chromatography over silica gel (gradient of methanol in dichloromethane) followed by a solidification in dichloromethane/ether provides 0.300 g (yield : 57%) of the desired product.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.28

NMR: DMSO ^{1}H δ (ppm): 3.55 (s,3H); 3.85 (s,3H); 4.45 (d,2H); 5.25 (s,2H); 7.3 (d,2H); 7.45 (d,2H); 7.60 (d,1H); 7.90 (d,2H); 8.15 (d,2H); 8.30 (s,1H); 8.65 (s,1H); 9.35 (t,1H).

IR : 1705, 1655, 1617, 1478, 1283, 750, 711 cm^{-1}

M.P. = 218 °C

HPLC : 99.1 %

Example 140 :4-{1-Methyl-2,4-dioxo-6-[(1-oxy-pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the Example 139.

NMR: DMSO ^{1}H δ (ppm): 3.55 (s,3H); 4.55 (d,2H); 5.20 (s,2H); 7.30-7.50 (m,4H); 7.60 (d,1H); 7.85 (d,2H); 8.25 (d,2H); 8.30 (d,1H); 8.65 (s,1H); 9.35 (t,1H); 12.9 (bs,1H).

IR : 1702, 1655, 1617, 1479, 1245, 753 cm^{-1}

M.P. = 192 °C

HPLC : 98.4 %

Example 141 :Methyl{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-3-benzyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-1-yl}-acetate

The compound is obtained by alkylation of the compound of Example 3 using K_2CO_3 and methylbromoacetate in DMF.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.70

NMR: DMSO ^{1}H δ (ppm): 3.70 (s,3H); 4.40 (d,2H); 5.05 (s,2H); 5.15 (s,2H); 6.0 (s,2H); 6.85 (m,3H); 7.30 (m,5H); 7.55 (d,1H); 8.20 (d,1H); 8.65 (s,1H); 9.20 (t,1H).

IR : 3282, 2361, 1736, 1669, 1632, 1464, 1370, 1236, 1040, 833, 776, 758 cm^{-1}

M.P. = 194.0 °C

HPLC : 97.6 %

Example 142 :{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-3-benzyl-2,4-dioxo-3,4-dihydro-2*H*-quinazolin-1-yl}-acetic acid

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the Example 141.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.70

NMR: DMSO ^{1}H δ (ppm): 4.35 (d,2H); 4.90 (s,2H); 5.15 (s,2H); 5.95 (s,2H); 6.80 (m,3H); 7.30 (m,5H); 7.50 (d,1H); 8.20 (d,1H); 8.60 (s,1H); 9.20 (t,1H); 13.25 (bs,1H).

IR : 3346, 2935, 1709, 1668, 1612, 1499, 1467, 1305, 1250, 1117, 1036, 873 cm^{-1}

M.P. = 163.0 °C

HPLC : 99.6 %

Example 143 :Methyl 4-{6-[(1,3-benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate

The compound is obtained according to the procedure of the Step 2 of the Example 34 using the compound obtained in the Example 37 and methyl 4-(bromomethyl)-benzoate.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.80

NMR: DMSO ^{1}H δ (ppm): 3.60 (s,3H); 3.90 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.0 (s,2H); 6.80-6.95 (m,3H); 7.45 (d,2H); 7.60 (d,1H); 7.85 (d,2H); 8.30 (d,1H); 8.65 (s,1H); 9.20 (t,1H).

IR : 3418, 1713, 1666, 1657, 1617, 1497, 1477, 1280, 1252, 1038, 770, 749 cm^{-1}

M.P. = 233.5 °C

HPLC : 99.6 %

Example 144 :4-{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the Example 143.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.40

NMR: DMSO ^{1}H δ (ppm) 3.60 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 5.95 (s,2H); 6.80-6.95 (m,3H); 7.40 (d,2H); 7.60 (d,1H); 7.85 (d,2H); 8.30 (d,1H); 8.60 (s,1H); 9.20 (t,1H); 12.85 (s,1H).

IR : 3377, 3233, 1717, 1698, 1665, 1649, 1502, 1481, 1236, 751 cm^{-1}

M.P. = 295.7 °C

HPLC : 97.9 %

Example 145: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-sulfamoyl-benzylamide

The compound is obtained according to the procedure of the Example 9 using the compound obtained in the Preparation C and 4-(aminomethyl)benzene sulfonamide hydrochlorhyde hydrate.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.37

NMR: DMSO ^1H δ (ppm): 3.60 (s,3H); 4.55 (d,2H); 5.15 (s,2H); 7.2- 7.35 (m,7H); 7.50 (d,2H); 7.60 (d,1H); 7.80 (d,2H); 8.30 (d,1H); 8.65 (s,1H); 9.35 (t,1H)

IR : 3290, 1709, 1652, 1618, 1503, 1321, 1154, 702 cm^{-1}

M.P. = 266 °C

HPLC : 97.5 %

Example 146 :3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid [3-(pyridin-4-ylsulfanyl)-propyl]-amide

The compound is obtained according to the procedure of the Example 9 using the compound obtained in the Preparation C, 3-(pyrydin-4-ylsulfanyl)-propylamine and dichloromethane as solvent. (The reactant 3-(pyridin-4-ylsulfamyl)-propylamine is obtained according to the method described in *Bioorg. Med. Chem.*, 1996, 4, 557-562).

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.70

NMR: DMSO ^1H δ (ppm): 1.8-1.90 (m,2H); 3.1-3.20 (m,2H); 3.4-3.50 (m,2H); 3.60 (s,3H); 5.20 (s,2H); 7.2- 7.40 (m,7H); 7.50-7.55 (m,1H); 8.20 (d,1H); 8.30-8.40 (m,2H); 8.60(s,1H); 8.80 (t,1H).

IR : 3308, 1705, 1662, 1636, 1578, 1509, 1447, 1321, 804, 712 cm^{-1}

M.P. = 130.7 °C

HPLC : 99.2 %

Example 147: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (4-morpholin-4-yl-butyl)-amide

The compound is obtained according to the procedure of the Step 3 of Example 116 using the compound obtained in the Preparation C, 4-morpholin-4-yl-butylamine, and dichloromethane as solvent. (The reactant 4-morpholin-4-yl-butylamine is obtained according to the method described in *J. Med. Chem.*, 1997, 40, 3915-3925).

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.60

NMR: DMSO ^1H δ (ppm): 1.4-1.60 (m,4H); 2.2-2.35 m,6H); 3.20-3.35 (m,2H); 3.55 (s,3H); 3.5-3.60 (m,4H); 5.20 (s,2H); 7.2-7.35 (m,5H); 7.50 (d,1H); 8.20-8.25 (m,1H); 8.60 (s,1H); 8.70 (t,1H)

IR : 3402, 2942, 1707, 1645, 1476, 1327, 1118, 763 cm^{-1}

M.P. = 170.6 °C

HPLC : 99.3 %

Example 148 :3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-benzyl-piperidin-4-yl)-amide

The compound is obtained according to the procedure of the Example 9 using the compound obtained in the Preparation C, 4-amino-1-benzylpiperidine, and dichloromethane as solvent. The desired compound crystallizes from amixture of dichloromethane and ether.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.50

NMR: DMSO ^1H δ (ppm): 1.60 (m,2H); 1.75 (m,2H); 2.0 (t,2H); 2.8 (d,2H); 3.45 (s,2H); 3.55 (s,3H); 3.75 (m,1H); 5.15 (s,2H); 7.30 (m,10H); 7.55 (d,1H); 8.20 (d,1H); 8.50 (d,1H); 8.60(s,1H).

IR : 3257, 2943, 2749, 1709, 1656, 1633, 1511, 1332, 1242, 1077, 829, 750 cm^{-1}

M.P. = 219.4 °C

HPLC : 98.6 %

Example 149 :3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-hydroxy-benzylamide

To a round bottom protected from moisture and under inert atmosphere are introduced 1.9 g (4.4 mmol) of compound of Example 13 in 200 ml of dichloromethane. To the stirred

solution are added dropwise 4.2 ml (11.1 g, 44 mmol) of BBr_3 in 17 ml of dichloromethane. After 30 minutes at room temperature the reaction mixture is poured to a 500 ml saturated solution of $NaHCO_3$, extracted with dichloromethane, dried and concentrated under vacuum. A crystallization of the crude product in methanol/ether provides 1.35 g (yield : 74%) of the desired compound.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.55

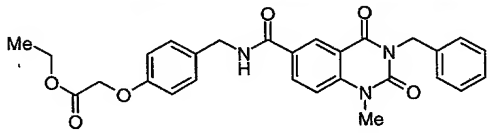
NMR: DMSO ^1H δ (ppm): 3.60 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.7-6.75 (m,2H); 7.10-7.20 (m,2H); 7.2-7.40 (m,5H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H); 9.0-9.3 (bs,1H).

IR : 3314, 1698, 1635, 1622, 1500, 1480, 1453, 1255, 826, 748 cm^{-1}

M.P. = 191.8 °C

HPLC : 96.4 %

Example 150 :Ethyl (4-{[(3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)-amino]-methyl}-phenoxy)-acetate



To a round bottom protected from moisture and under inert atmosphere are introduced 0.45 g (1.08 mmol) of compound of Example 149 in 13.5 ml od DMF. To the stirred solution are added 0.3 g of K_2CO_3 (2.16 mmol) and 0.24 ml (2.016 mmol) of ethyl bromoacetate. After 1 hour at 60°C the reaction mixture is concentrated under vacuum. The crude product is taken up in dichloromethane, washed with water, dried and concentrated under vacuum to provide 0.410 g (yield : 75.8%) of the desired compound.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.70

NMR: DMSO ^1H δ (ppm): 1.2 (t,3H); 3.60 (s,3H); 4.15 (q,2H); 4.45 (d,2H); 4.80 (s,2H); 5.20 (s,2H); 6.90 (d,2H); 7.2-7.40 (m,7H); 7.5 (d,1H); 8.20 (d,1H); 8.60 (s,1H); 9.20 (t,1H)

IR : 3407, 1755, 1705, 1642, 1508, 1324, 1210, 750 cm^{-1}

M.P. = 172.6 °C

HPLC : 97.8 %

Example 151 :(4-{[(3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-

carbonyl)-amino]-methyl}-phenoxy)-acetic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound of the Example 150.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.70

NMR: DMSO ^1H δ (ppm): 3.60 (s,3H); 4.40 (d,2H); 4.65 (s,2H); 5.15 (s,2H); 6.85 (d,2H); 7.2-7.40 (m,7H); 7.55 (d,1H); 8.25 (d,1H); 8.65 (s,1H); 9.20 (t,1H); 12.95 (bs,1H).

IR : 3407, 1755, 1705, 1642, 1508, 1324, 1210, 750 cm^{-1}

M.P. = 195.6 °C

HPLC : 98.3 %

Example 152 :3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-dimethylcarbamoylmethoxy-benzylamide

The compound is obtained according to the procedure of the Example 1 using the compound of Example 151 and dimethylamine 2M in solution in THF.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.70

NMR: DMSO ^1H δ (ppm): 2.80 (s,3H); 3.0 (s,3H); 3.55 (s,3H); 4.40 (d,2H); 4.80 (s,2H); 5.20 (s,2H); 6.90 (d,2H); 7.2-7.40 (m,7H); 7.50 (d,1H); 8.20 (d,1H); 8.65 (s,1H); 9.25 (t,1H).

IR : 3276, 1704, 1659, 1635, 1499, 1317, 1240, 1066, 750 cm^{-1}

M.P. = 152.7 °C

HPLC : 96.5 %

Example 153: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (3-phenyl-allyl)-amide

The compound is obtained according to the procedure of the Example 9 using the compound of the Preparation C and 3-phenyl-allylamine hydrochloride.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.80

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 4.10 (m,2H); 5.20 (s,2H); 6.35 (m,1H); 6.60 (m,1H); 7.20-7.35 (m,8H); 7.40 (m,2H); 7.55 (d,1H); 8.30 (d,1H); 8.70 (s,1H); 9.00 (m,1H).

M.P. = 193.0 °C

HPLC : 99.7 %

Example 154 :3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-cyano-benzylamide

The compound is obtained according to the procedure of the Example 9 using the compound of the Preparation C and 4-amino-benzyl benzonitrile. The desired product is solidified in a mixture of dichloromethane/ether.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.46

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 4.60 (d,2H); 5.15 (s,2H); 7.20-7.40 (m,5H); 7.45-7.60 (m,3H); 7.80 (d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.40 (t,1H).

IR : 3305, 2224, 1708, 1664, 1638, 1507, 1318, 751 cm^{-1}

M.P. = 245.0 °C

HPLC : 96.2 %

Example 155 :4-{[(3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)-amino]-methyl}-benzoic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound of the Example 11.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.30

NMR: DMSO ^1H δ (ppm): 3.55 (s,3H); 4.55 (d,2H); 5.15 (s,2H); 7.25 (m,5H); 7.40 (d,2H); 7.55 (d,1H); 7.90(d,2H); 8.25 (d,1H); 8.65 (s,1H); 9.30 (t,1H); 12.90 (bs,1H).

IR : 3395, 1707, 1698, 1642, 1618, 1501, 1431, 1291, 1242, 938, 829, 759 cm^{-1}

M.P. = 228.5 °C

HPLC : 96.9 %

Example 156 :3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-dimethylcarbamoyl-benzylamide

The compound is obtained according to the procedure of the Example 1 using the compound of the Example 155 and dimethylamine in solution 2M in THF.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.70

NMR: DMSO ^1H δ (ppm): 3.0 (m,6H); 3.55 (s,3H); 4.55 (d,2H); 5.15 (s,2H); 7.30 (m,9H); 7.60 (d,1H); 8.30 (d,1H); 8.65 (s,1H); 9.30 (t,1H).

IR : 3249, 2361, 1705, 1657, 1609, 1504, 1452, 1254, 1069, 1020, 839, 750 cm^{-1}

M.P. = 194.7 °C

HPLC : 96.8 %

Example 157 :3-(4-Dimethylamino-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the Step 1-5 to 3-5 of the preparation B using in the Step 1-5 4-dimethylamino-benzyl isocyanate, and then according to the procedure of Example 1 using the compound obtained in the preceding step and 4-methoxy-benzylamine

NMR: DMSO ^1H δ (ppm): 2.80 (s,6H); 3.70 (s,3H); 4.40 (d,2H); 4.95 (s,2H); 6.60 (d,2H); 6.85 (d,2H); 7.15-7.25 (m,5H); 8.10 (dd,1H); 8.50 (s,1H); 9.10 (t,1H); 11.7 (s,1H).

IR : 3177, 1729, 1630, 1512, 1445, 1249, 765 cm^{-1}

M.P. = 267 °C

HPLC: 98.5%

Example 158 :3-[4-(N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Example 97 using as substrates the compound obtained in the Example 95 and 2.5 equivalents of methanesulfonyl chloride.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.22

NMR:.DMSO ^{1}H δ (ppm) : 2.90 (s,3H); 3.55 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.10 (s,2H); 6.90 (d,2H); 7.10 (d,2H) ; 7.25 (d,2H); 7.30 (d,2H); 7.55 (s,1H); 8.25 (d,1H); 8.60 (s,1H); 9.2 (t,1H); 9.70 (s,1H)

IR : 1655, 1615, 1513, 1500, 1325, 1248, 1148 cm^{-1}

M.P. = 224 °C

HPLC : 98.8 %

Example 159: tert-Butyl {5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-pyridin-2-yl}-carbamate

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and *tert*-butyl (5-bromomethyl-pyridin-2-yl)-carbamate.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.80

NMR:.DMSO ^{1}H δ (ppm) : 1.45 (s,9H); 3.55 (s,3H); 3.75 (s,3H); 4.40 (d,2H); 5.10 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,1H); 7.70 m,2H); 8.25-8.30 (m,2H); 8.65 (s,1H); 9.2 (t,1H); 9.70 (s,1H)

IR : 1711, 1654, 1614, 1508, 1478, 1302, 1243, 1159 cm^{-1}

M.P. = 204 °C

HPLC : 99.3 %

Example 160: 3-(6-Amino-pyridin-3-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained by deprotection of compound of the Example 159 by using trifluoroacetic acid in dichloromethane.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.40

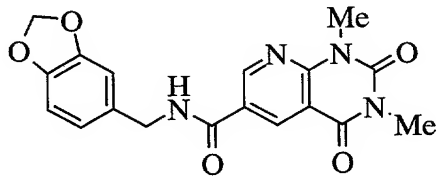
NMR:.DMSO ^{1}H δ (ppm) : 3.55 (s,3H); 3.75 (s,3H); 4.40 (d,2H); 4.95 (s,2H); 5.80 (bs,2H); 6.35 (d,1H); 6.90 (d,2H); 7.25 (d,2H); 7.40 (dd,1H); 7.50 (d,1H); 7.95 (s,1H); 8.25 (dd,1H); 8.60 (s,1H); 9.2 (t,1H)

IR : 1704, 1648, 1615, 1509, 1477, 1245 cm^{-1}

M.P. = 155°C

HPLC : 99.5 %

Example 161 :1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide



Step 1 :1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid.

The compound is obtained by hydrolysis in a mixture of dioxan/water of ethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylate (*Heterocycles* 1998, 48(12),2521-2528) in presence of LiOH.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.10

R.M.N:.DMSO ^1H δ (ppm): 3.30 (s,3H) ; 3.60 (s,3H) ; 8.70 (s,1H) ; 9.15 (s,1H) ; 13.5 (bs,1H)

Step 2: 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 1 and piperonylamine.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.90

NMR:.DMSO ^1H δ (ppm): 3.35 (s,3H); 3.6 (s,3H); 4.40 (d,2H); 6.0 (s,2H); 6.75-6.85 (m,2H); 6.90 (s,1H); 8.80 (s,1H); 9.15 (s,1H); 9.30 (t,1H).

IR : 3227, 1705, 1663, 1632, 1608, 1498, 1299, 1250, 1040, 794 cm^{-1}

M.P. = 218.4°C

HPLC : 94.6 %

Example 162: 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

Step 1 : 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid

The compound is obtained by hydrolysis in a mixture of dioxan/water of methyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylate (*Heterocycles* 1994, 37(1), 563-570) in presence of LiOH.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.01

NMR:.DMSO ^1H δ (ppm): 3.30 (s,3H); 3.60 (s,3H); 8.40 (s,1H); 9.00 (s,1H); 13.3 (bs,1H)

Step 2: 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 1 and piperonylamine.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.90

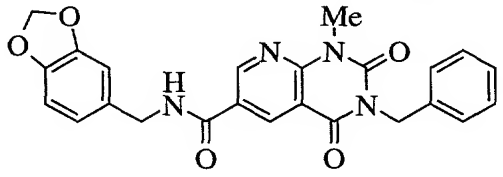
NMR:.DMSO ^1H δ (ppm): 3.35 (s,3H); 3.65 (s,3H); 4.45 (d,2H); 6.0 (s,2H); 6.80-6.90 (m,2H); 6.95 (s,1H); 8.50 (s,1H); 8.95 (s,1H); 9.25 (t,1H).

IR : 3379, 1713, 1662, 1478, 1253, 1238, 924, 750 cm^{-1}

M.P. = 288.7°C

HPLC : 96.3 %

Example 163: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*] pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide



Step 1: N'-(1-Benzyl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl)-N,N-dimethyl-formamidine

0.56 g (2.5 mmol) of 6-amino-3-benzyl-1*H*-pyrimidine-2,4-dione (Tetrahedron Letters, 1991, 32(45), 6534-6540) in 20 ml of DMF are strirred under inert atmosphere. 1 ml (7.5 mmol) of *N,N'*-dimethylformamide dimethyl acetal is added to this solution and the mixture is heated to reflux for 20 minutes. After cooling and concentration under vacuum, the residue is taken up in dichloromethane, and the organic phase is washed with water,

dried over Na_2SO_4, and concentrated under vacuum until a low volume. Then the crude product is precipitate by addition of ether. After filtration 0.680g (yield : 72.6%) of the desired compound is obtained.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.80

NMR:.DMSO ^1H δ (ppm): 3.0 (s,3H); 3.15 (s,3H); 3.30 (s,3H); 4.90 (s,2H); 5.20 (s,1H); 7.2-7.35 (m,5H) ; 8.10 (s,1H)

Step 2: *N'*-(1-Benzyl-5-iodo-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl)-*N,N*-dimethyl-formamidine

To a stirred solution of 0.68 g (2.38 mmol) of the compound obtained in the preceding Step 1 in 24 ml of anhydrous dichloromethane is added 0.64 g (2.85 mmol) of N-iodosuccinimide. After 30 minutes of reflux, the reaction mixture is cooled and the organic phase is washed with water, dried over Na_2SO_4, and concentrated under vacuum. The crude product is precipitated in ether to obtain 0.680 g (yield: 69.3%) of the desired compound.

NMR:.$CDCl_3$ ^1H δ (ppm): 3.05 (s,3H) ; 3.15 (s,3H) ; 3.40 (s,3H) ; 5.20 (s,2H) ; 7.2-7.30 (m,3H) ; 7.5-7.55 (m,2H) ; 7.7 (s,1H).

M.P. = 186.3°C

Step 3: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine -6-carboxylic acid ethyl ester

To a stirred solution of 0.68 g (1.65 mmol) of the compound obtained in the preceding Step 2 in 45 ml of anhydrous DMF are added successively 18 mg $Pd(OAc)_2$, 8 mg of CuI, 330 mg of K_2CO_3, and 0.22 ml of ethyl acrylate. After 30 minutes under reflux, the reaction mixture is concentrated under vacuum. The residue is taken up in dichloromethane. The organic phase is filtered, washed two times with water, dried over Na_2SO_4 and then concentrated under vacuum. The crude product is purified by chromatography over silica gel (dichloromethane/methanol : 97/3) and then crystallized from ether to give 0.320 g (yield:57%) of the desired compound.

TLC : CH_2Cl_2 / MeOH 97.5/2.5 Rf = 0.50

NMR: $CDCl_3$ ^1H δ (ppm): 1.40 (t,3H) ; 3.70 (s,3H) ; 4.40 (q,2H) ; 5.30 (s,2H) ; 7.2-7.30 (m,3H) ; 7.5-7.55 (m,2H) ; 9.0 (s,1H) ; 9.2 (s,1H)

Step 4: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine -6-carboxylic acid

The compound is obtained by hydrolysis, in a mixture of dioxan/water in presence of LiOH, of the compound obtained in the preceding Step 3.

TLC : CH_2Cl_2 / MeOH 90 / 10 Rf = 0.10

NMR:.DMSO ^1H δ (ppm): 3.60 (s,3H) ; 5.20 (s,2H) ; 7.2-7.40 (m,5H) ; 8.75 (s,1H) ; 9.2 (s,1H) ; 13.5 (bs,1H)

HPLC = 100%

Step 5: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine -6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 4 and piperonylamine.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.60

NMR:.DMSO ^1H δ (ppm): 3.60 (s,3H); 4.40 (d,2H); 5.2 (s,2H); 5.95 (s,2H); 6.75-6.95 (m,3H); 7.2-7.40 (m,5H); 8.85 (s,1H); 9.2 (s,1H); 9.25 (t,1H).

IR : 3271, 1709, 1665, 1630, 1614, 1488, 1248, 1042, 937, 795 cm^{-1}

M.P. = 174.9°C

HPLC : 97.5 %

Example 164: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid

Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid

A solution of 1.3 g (4.17 mmol) of the compound obtained in the Step 4 of Example 163 and 3.1 g (23 mmol) of $AlCl_3$ in 44 ml of benzene is stirred 2 hours at room temperature. After addition of a mixture water/ice, the reaction mixture is extracted successively with

ethyl acetate and dichloromethane. The aqueous layer is acidified at pH 1 by addition of concentrated HCl. The precipitate obtained is filtered off and washed with 10 ml of methanol and 10 ml of dichloromethane to provide the desired compound (yield: 62.9%)

NMR:.DMSO ^1H δ (ppm): 3.50 (s,3H) ; 8.60 (s,1H) ; 9.10 (s,1H) ; 11.9 (bs,1H) ; 13.5 (bs,1H)

HPLC = 100%

Step 2: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 2 and 4-methoxybenzylamine.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.45

NMR:.DMSO ^1H δ (ppm): 3.50 (s,3H); 3.7 (s,3H); 4.40 (d,2H); 6.85-6.95 (m,2H); 7.25-7.30 (m,2H) ; 8.80 (s,1H) ; 9.15 (s,1H) ; 9.30 (t,1H) ; 11.85 (bs,1H)

HPLC = 92%

Step 3: Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the preceding Step 2 and methyl-4-(bromomethyl)benzoate. After concretization in ether 0.41 g (yield: 71.1%) of the desired compound is isolated.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.80

NMR:.DMSO ^1H δ (ppm): 3.60 (s,3H) ; 3.80 (s,3H) ; 3.90 (s,3H) ; 4.45 (d,2H) ; 5.2 (s,2H) ; 6.90 (dd,2H) ; 7.30 (dd,2H) ; 7.50 (dd,2H) ; 7.90 (dd,2H) ; 8.90 (s,1H) ; 9.20 (s,1H) ; 9.30 (t,1H) ;

HPLC = 96.8%

Step 4: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid

The compound is obtained according to the procedure of Example 35 using the compound obtained in the preceding Step 3.

NMR:.DMSO ^{1}H δ (ppm): 3.60 (s,3H); 3.70 (s,3H); 4.45 (d,2H) ; 5.20 (s,2H) ; 6.90 (d,2H); 7.25 (d,2H); 7.45 (d,2H); 7.90 (d,2H); 8.85 s,1H); 9.20 (s,1H); 9.30 (t,1H) ; 12.90 (bs,1H)

IR : 3292, 1718, 1695, 1667, 1633, 1609, 1497, 1301, 1242, 797 cm^{-1}

M.P. = 229.5 °C

HPLC : 93.6 %

Example 165: 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido [2,3-*d*] pyrimidine-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained (0.11 g ; yield=68.4%) according to the procedure of the Step 2 of Example 34 using the compound obtained in Step 2 of Example 164 and 4-(bromomethyl)benzonirile.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.70

NMR:.DMSO ^{1}H δ (ppm): 3.60 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.20 (s,2H); 6.90 (d,2H); 7.30 (d,2H); 7.55 (d,2H); 7.80 (d,2H); 8.85 (s,1H); 9.20 (s,1H); 9.30 (t,1H)

IR : 3230, 2230, 1710, 1673, 1635, 1609, 1494, 1303, 1252, 794 cm^{-1}

M.P. = 197 °C

HPLC : 97.2 %

Example 166: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido [2,3-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in Step 2 of Example 164 and 4-fluorobenzyl bromide.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.70

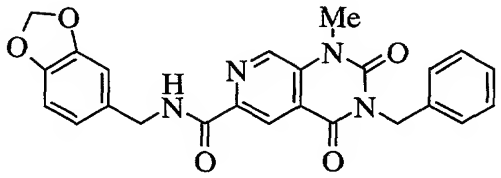
NMR:.DMSO ^{1}H δ (ppm): 3.60 (s,3H); 3.70 (s,3H); 4.40 (d,2H); 5.10 (s,2H); 6.8-6.90 (m,2H); 7.1-7.2 (m,2H); 7.25-7.35 (m,2H); 7.4-7.50 (m,2H); 8.85 (s,1H); 9.15 (s,1H); 9.30 (t,1H).

IR : 3260, 1709, 1664, 1616, 1497, 1245, 1221, 1035, 796 cm^{-1}

M.P. = 211.5 °C

HPLC : 98.3 %

Example 167: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*] pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide



Step 1 : 1-Benzyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carbaldehyde

A solution of 9.5 g (43.9 mmol) of 3-benzyl-6-methyl-1*H*-pyrimidine-2,4-dione (*Synthetic Communications* 1991, 2181-2188) and 129 ml of cold acetic acid are stirred 5 minutes, and 5.75 g of SeO_2 are added. The reaction mixture is heated to reflux for 2h30, filtered and concentrated under vacuum. The residue is taken up in dichloromethane. The unsoluble part is eliminated and the filtrate is concentrated under vacuum. A chromatography over silica gel (dichloromethane/methanol : 95/5) provides 4.0 g of the desired compound (yield:39.5%).

NMR:.$CDCl_3$ ^1H δ (ppm): 5.20 (s,2H); 6.30 (s,1H); 7.2-7.30 (m,3H); 7.40-7.50 (m,2H); 9.0 (bs,1H); 9.60 (s,1H)

Step 2: 1-Benzyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carbaldehyde dimethylhydrazone

To a stirred solution of 3.6 g (15.6 mmol) ofthe compound obtained in the preceding Step 1 in 80 ml of anhydrous DMF are added 1.2 ml (0.94 g, 15.6 mmol) of dimethylhydrazine. After 1 hour of stirring at room temperature, the solvent is removed under vacuum and the residue is taken up in dichloromethane. The organic layer is washed, dried over Na_2SO_4 and concentrated. A chromatography over silica gel (dichloromethane/methanol : 97/3) provides 2.5 g (yield:59%) of the desired compound.

NMR:.$CDCl_3$ ^1H δ (ppm) 3.10 (s,6H);5.10 (s,2H); 5.55 (s,1H); 6.50 (s,1H); 7.2-7.30 (m,3H); 7.40-7.50 (m,2H); 8.50 (bs,1H)

Step 3 : 1-Benzyl-2,6-dioxo-3-methyl-1,2,3,6-tetrahydro-pyrimidine-4-carbaldehyde dimethylhydrazone

To a stirred solution of 2.3 g (8.45 mmol) of the compound obtained in the preceding Step 2 in 58 ml of anhydrous DMF are added 2.3 ml (2.0 g, 1.69 mmol) of *N,N'*-dimethylformamide acetal. The reaction mixture is maintained at 100°C for 10 minutes and concentrated under vacuum. The residue is taken up in dichloromethane and the product is precipitated by addition of ether to provide 1.75 g (yield:72.3%) of the desired compound.

NMR:. $CDCl_3$ ^1H δ (ppm) 3.20 (s,6H) ;3.50 (s,3H) ; 5.15 (s,2H) ; 6.10 (s,1H) ; 6.60 (s,1H) ; 7.2-7.30 (m,3H) ; 7.40-7.50 (m,2H)

Step 4: Methyl 1-benzyl-2,6-dioxo-3-methyl-1,2,3,6-tetrahydro-pyrimidine-4-(carbaldehyde dimethylhydrazone)-5-carboxylate

To a stirred solution of 1.7 g (5.94 mmol) of the compound obtained in the preceding Step 3 in 61 ml of anhydrous acetonitrile are added successively 1.68 g (7.1 mmol) of $Pd(OAc)_2$ and 0.613 g (7.1 mmol) of methyl acrylate. After 20 minutes od stirring under reflux the reaction mixture is filtered off and oncentrated under vacuum. The residue is chromatographied over silica gel (dichloromethane/methanol : 97/3) to provide 1.40 g (yield:63.6%) of the desired compound.

NMR:. $CDCl_3$ ^1H δ (ppm): 3.20 (s,6H) ;3.55 (s,3H) ; 3.75 (s,3H) ; 5.20 (s,2H) ; 6.70 (s,1H) ; 7.1 -7.70 (m,7H).

Step 5: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine -6-carboxylic acid methyl ester

A solution of 1.4 g (3.78 mmol) of the compound obtained in the preceding Step 4, 18 ml of chlorobenzene and 3.6 ml of acetic acid is stirred under reflux for 3 hours, and concentrated under vacuum to provide 1.4 g of a precipitate. The desired compound (0.76 g; yield:62%) is obtained by recrystallization of the crude product in 120 ml of ethyl acetate.

NMR:. $CDCl_3$ ^1H δ (ppm): 3.70 (s,3H) ;4.0 (s,3H) ; 5.30 (s,2H) ; 7.2-7.35 (m,3H) ; 7.45-7.55 (m,2H) ; 8.80 (s,1H) ; 8.85 (s,1H).

Step 6: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine -6-carboxylic acid

0.76 g (2.34 mmol) of the compound obtained in the preceding Step 5, 7.6 ml of methanol, 7.6 ml of water and 0.646 g (4.67 mmol) of K_2CO_3 are stirred overnight at room temperature and then heated to reflux for 5 minutes. After cooling and addition of water the acification to pH 1 of the mixture provides a precipitate which is dissolved in a mixture of methanol/dichloromethane. The organic layer is washed with water, dried and concentrated under vacuum. The residue obtained is concretized in a mixture of dichloromethane/ether to give 0.54 g (yield: 74%) of the desired compound.

NMR:.DMSO ^1H δ (ppm) 3.60 (s,3H); 5.20 (s,2H); 7.2-7.40 (m,5H); 8.50 (s,1H); 9.0 (s,1H) ; 13.3 (bs,1H)

M.P. = 240°C

HPLC = 100%

Step 7: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine -6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 6 and piperonylamine.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.60

NMR:.DMSO ^1H δ (ppm): 3.65 (s,3H); 4.40 (d,2H) ; 5.15 (s,2H) ; 5.95 (s,2H); 6.75-6.85 (m,2H); 6.90 (s,1H); 7.2-7.40 (m,5H); 8.45 (s,1H); 8.90 (s,1H); 9.25 (t,1H).

IR : 3387, 1716, 1662, 14875, 1442, 1250, 1239, 1040, 789 cm^{-1}

M.P. = 197.5 °C

HPLC : 100 %

Example 168 :Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoate

Step 1 : 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid

3.3 g (10.6 mmol) of the compound obtained in the Step 6 of Example 167 are treated according to the procedure described in the Step 1 of Example 164 to give 2.0 g (yield: 85.3%) of the desired compound.

NMR:.DMSO ^1H δ (ppm): 3.60 (s,3H) ; 8.40 (s,1H) ; 8.95 (s,1H) ; 12.0 (s,1H) ; 12.90 (bs,1H)

HPLC = 100%

Step 2: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained (yield: 78%) according to the procedure of the Example 1 using the compound obtained in the preceding Step 1 and 4-methoxybenzylamine.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.50

NMR:.DMSO ^1H δ (ppm): 3.60 (s,3H) ; 3.75 (s,3H) ; 4.40 (d,2H) ; 6.85 (dd,2H) ; 7.25 (dd,2H) ; 8.40 (s,1H) ; 8.85 (s,1H) ; 9.20 (t,1H) ; 12.0 (s,1H)

HPLC = 99 %

Step 3: Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoate

The compound is obtained (0.2 g; yield:77%) according to the procedure of the Step 2 of Example 34 using the compound obtained in the preceding Step 2 and methyl-4-(bromomethyl)benzoate.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.80

NMR:.DMSO ^1H δ (ppm): 3.60 (s,3H); 3.70 (s,3H); 3.85 (s,3H); 4.50 (d,2H) ; 5.20 (s,2H) ; 6.85 (d,2H); 7.20 (d,2H); 7.50 (d,2H); 7.90 (d,2H); 8.5 (s,1H); 8.90 (s,1H); 9.20 (t,1H)

IR : 3396, 1719, 1661, 1439, 1279, 1250, 1110, 753 cm^{-1}

M.P. = 211.1 °C

HPLC : 99.5 %

Example 169: tert-Butyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoate

The compound is obtained (yield: 80.4%) according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 2 of example 168 and *tert*-butyl 4-bromomethyl-benzoate.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.80

NMR:.DMSO ^1H δ (ppm): 1.50 (s,9H) ; 3.65 (s,3H) ; 3.75 (s,3H) ; 4.40 (d,2H) ; 5.20 (s,2H) ; 6.85 (dd,2H) ; 7.25 (dd,2H) ; 7.45 (dd,2H) ; 7.85 (dd,2H) ; 8.50 (s,1H) ; 8.90 (s,1H) ; 9.2 (t,1H) ;

HPLC = 98 %

Example 170: 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid

Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide

The compound is obtained (yield: 62.4%) according to the procedure of the Example 1 using the compound obtained in the Step 1 of Example 168 and 3-methoxybenzylamine.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.50

NMR:.DMSO ^1H δ (ppm): 3.60 (s,3H) ; 3.75 (s,3H) ; 4.50 (d,2H) ; 6.75-6.95 (m,3H) ; 7.20-7.30 (m,1H) ; 8.40 (s,1H) ; 8.85 (s,1H) ; 9.25 (t,1H) ; 12.0 (s,1H)

HPLC = 98 %

Step 2: *tert*-Butyl 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoate

The compound is obtained (yield: 80.4%) according to the procedure of the Step 2 of Example 34 using the compound obtained in the preceding Step 1 and *tert*-butyl 4-(bromomethyl)benzoate.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.80

NMR:.DMSO ^1H δ (ppm): 1.50 (s,9H) ; 3.65 (s,3H) ; 3.75 (s,3H) ; 4.50 (d,2H) ; 5.20 (s,2H) ; 6.80-6.95 (m,3H) ; 7.20-7.30 (m,1H) ; 7.5 (dd,2H) ; 7.85 (dd,2H) ; 8.50 (s,1H) ; 8.95 (s,1H) ; 9.3 (t,1H) ;

HPLC = 93.6 %

Step 3: 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid

The compound is obtained according to the procedure of the Step 2 of Example 169 using the compound obtained in the preceding Step 2.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.60

NMR:.DMSO ^1H δ (ppm): 3.65 (s,3H); 3.75 (s,3H); 4.50 (d,2H) ; 5.20 (s,2H) ; 6.75-6.80 (s,1H); 6.90 (s,2H); 7.20-7.25 (m,1H); 7.45 (d,2H); 7.85 (d,2H); 8.5 (s,1H); 8.90 (s,1H); 9.30 (t,1H); 12.95 (bs,1H)

IR : 3378, 1712, 1660, 1600, 1439, 1266, 1056, 790 cm^{-1}

M.P. = 208.1 °C

HPLC : 96.6 %

Example 171: 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 2 of Example 168 and (4-bromomethyl)-benzonitrile

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.80

NMR:.DMSO ^1H δ (ppm): 3.65 (s,3H); 3.75 (s,3H); 4.45 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.55 (d,2H); 7.80 (d,2H); 8.5 (s,1H); 8.95 (s,1H); 9.20 (t,1H).

IR : 3391, 2228, 1716, 1662, 1443,1331, 1251, 789 cm^{-1}

M.P. = 230 °C

HPLC : 98.8 %

Example 172: 3-Benzyl-1-methyl-6-(3-phenyl-propionyl)-1H-quinazoline-2,4-dione

The compound of the preparation C is treated by $SOCl_2$ in THF to give its chloride derivate which is reacted with phenetyl magnesium bromide and CuI in presence of THF. After usual treatment the desired compound is obtained.

NMR:.$CDCl_3$ ^1H δ (ppm): 3.0 (m,2H); 3.30 (m,2H); 3.60 (s,3H); 5.25 (s,2H) ; 7.10-7.35 (m,9H); 7.50 (m,2H); 8.3 (m,1H); 8.80 (s,1H)

M.P. = 155 °C

HPLC : 98.0 %

Example 173: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (E)-3-pyridin-4-yl-allyl ester

NMR:.$CDCl_3$ ^1H δ (ppm) 3.60 (s,3H) ; 5.0 (d,2H) ; 5.30 (s,2H) ; 6.5-6.7 (m,2H); 7.15-7.35 (m,6H); 7.55 (m,2H) ; 8.40 (m,1H); 8.60 (m,2H) ; 9.0 (s,1H)

M.P. = 147 °C

HPLC : 97.5 %

Example 174: 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (E)-3-pyridin-3-yl-allyl ester

NMR:.$CDCl_3$ ^1H δ (ppm): 3.60 (s,3H) ; 5.0 (d,2H) ; 5.30 (s,2H) ; 6.5 (m,1H) ; 6.8 (d,1H); 7.30 (m,5H); 7.60 (m,2H) ; 7.7 (d,1H) ; 8.40 (d,1H); 8.55 (m,1H) ; 8.70 (s,1H) ; 9.0 (s,1H)

M.P. = 184 °C

HPLC : 99.6 %

Example 175: 3-Benzyl-1-methyl-6-[2-(pyridin-4-ylsulfanyl)-acetyl]-1*H*-quinazoline-2,4-dione

TLC : CH_2Cl_2 / MeOH 98/2 Rf = 0.20

NMR:.CDCl3 ^1H δ (ppm): 3.65 (s,3H); 4.45 (s,2H) ; 5.25 (s,2H) ; 7.18 (d,2H); 7.20-7.35 (m,4H) ; 7.50 (d,2H); 8.3 (d,1H); 8.40 (d,2H); 8.80 (s,1H).

IR :1706, 1693, 1657, 1610, 1574, 1508, 1480, 1448, 1428, 1321, 1307, 1206, 1093, 831, 810, 782, 703 cm^{-1}

M.P. = 187 °C

HPLC : 98.0 %

Example 176: 3-(4-Aminomethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained by catalytic hydrogenation of the compound of Example 60 using Raney Ni and NH_3 in methanol.

TLC : CH_2Cl_2 / MeOH / NH_4OH 90/10 /1 Rf = 0.25

NMR:.$CDCl_3$ ^1H δ (ppm): 1.45-1.70 (m,2H) ; 3.6 (s,3H) ; 3.8 (m,5H) ; 4.55 (d,2H) ; 5.22 (s,2H) ; 6.74 (m,1H) ; 6.86 (d,2H) ; 7.2-7.30 (m,5H) ; 7.44 (d,2H) ; 8.28 (d,1H) ; 8.48 (s,1H)

IR : 3370, 1702, 1655, 1640, 1617, 1542, 1508, 1477, 1324, 1303 ; 1247, 1173, 1032, 829, 786, 756 cm^{-1}

M.P. = 187 °C

HPLC : 98.4%

Example 177: 3-(2'-Cyano-biphenyl-4-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of Example 34 using 2-(4-bromomethylphenyl)-benzonitrile.

TLC : CH_2Cl_2 / MeOH 98.5/1.5 Rf = 0.20

NMR:.$CDCl_3$ ^1H δ (ppm): 3.65 (s,3H) ; 3.80 (s,3H) ; 4.55 (d,2H) ; 5.30 (s,2H) ; 6.55-6.65 (m,1H) ; 6.25 (d,2H) ; 7.2-7.30 (m,3H) ; 7.35-7.50 (m,4H) ; 7.55-7.65 (m,3H) ; 7.75 (d,1H) ; 8.25-8.35 (m,1H) ; 8.45 (s,1H)

IR : 1702, 1661, 1629, 1508, 1478, 1332, 1242, 1036, 833, 766 cm^{-1}

M.P. = 200 °C

HPLC : 99.8 %

Example 178: 1-Methyl-2,4-dioxo-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of Example 34 using 5-[(4-bromomethyl)biphenyl]-tetrazole.

TLC: CH_2Cl_2 / MeOH 90/10 Rf = 0.50

NMR:.DMSO ^1H δ (ppm): 3.55 (s, 3H) ; 3.75 (s,3H) ; 4.40 (d,2H) ; 5.15 (s,2H) ; 6.90 (d,2H) ; 7.05 (d,2H) ; 7.25 (d,4H) ; 7.45-7.70 (m,6H) ; 8.30 (d,1H) ; 8.6 (s,1H) ; 9.25 (m,1H)

IR : 2943, 1702, 1656, 1618, 1510, 1477, 1450, 1323, 1302, 1247, 1032, 829, 814, 782, 757 cm^{-1}

HPLC : 99.6 %

Example 179: Methyl 4'-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-biphenyl-2-carboxylate

The compound is obtained according to the procedure of the Step 2 of Example 34 using Methyl 4-(bromomethylphenyl)benzoate

TLC: CH_2Cl_2 / MeOH 97/3 Rf = 0.30

NMR: DMSO ^1H δ (ppm): 3.61 (s,3H) ; 3.62 (s,3H) ; 3.80 (s,3H) ; 4.55 (d,2H) ; 5.30 (s,2H) ; 6.65 (t,1H) ; 6.85(d,2H) ; 7.2-7.30 (m,6H) ; 7.35-7.40 (m,1 H) ; 7.45-7.55 (m,3H) ; 7.80 (d,1H) ; 8.27 (d,1H) ; 8.47 (s,1H)

IR : 1707, 1668, 1656, 1638, 1616, 1509, 1478, 1330, 1294, 1248, 1089, 765, 754 cm^{-1}

M.P. = 172 °C

HPLC : 99.7 %

Example 180: 4'-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-biphenyl-2-carboxylic acid

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound of Example 179.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.40

NMR:.DMSO ^1H δ (ppm): 3.57 (s,3H) ; 3.72 (s,3H) ; 4.42 (d,2H) ; 5.20 (s,2H) ; 6.90 (d,2H) ; 7.25-7.45 (m,8H) ; 7.50-7.60 (m,2 H) ; 7.70 (d,1H) ; 8.26 (d,1H) ; 8.60 (s,1H) ; 9.17-9.27 (m,1H) ; 12.5-13.2 (m,1H)

IR : 1698, 1668, 1655, 1639, 1612, 1508, 1479, 1330, 1304, 1248, 765, 754 cm^{-1}

M.P. = 175 °C

HPLC : 100 %

Example 181: Ethyl 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 2 of Example 34 using Methyl 4-(bromomethyl)-2-fluoro-benzoate.

TLC: CH_2Cl_2 / MeOH 90/10 Rf = 0.60

NMR: $CDCl_3$ ^1H δ (ppm): 1.30 (t,3H) ; 3.60 (s,3H) ; 3.80 (s,3H) ; 4.35 (q,2H) ; 4.60 (m,2H) ; 5.30 (s,2H) ; 6.55 (m,1H) ; 6.90 (m,2H) ; 7.30 (m,5H) ; 7.90 (m,1H) ; 8.30 (m,1H) ; 8.50 (s,1H) ;

M.P. = 156 °C

HPLC : 100 %

Example 182: 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound of Example 181.

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.20

NMR:.DMSO ^1H δ (ppm): 3.60 (s,3H) ; 3.75 (s,3H) ; 4.40 (m,2H) ; 5.20 (s,2H) ; 6.90 (m,2H) ; 7.30 (m,4H) ; 7.60 (d,1H) ; 7.80 (m,1H) ; 8.30 (m,1H) ; 8.70 (s,1H) ; 9.2 (s,1H) ; 13.2 (s,1H)

M.P. = 160 °C

HPLC : 100 %

Example 183: 2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.20

NMR:.$CDCl_3$ ^1H δ (ppm) 2.3 (s,6H) ; 2.60 (m,2H) ; 3.60 (s, 3H) ; 3.75 (s,3H) ;3.85 (s,3H) ; 4.35 (m,2H) ; 4.55 (m,2H) ; 5.25 (s,2H) ; 6.50 (m,1H) ; 6.80 (m,2H) ; 7.10 (d,1H) ; 7.25 (m,4H) ; 7.70 (d,1H) ; 8.25 (m,1H) ; 8.5 (s,1H)

M.P. = 130 °C

HPLC : 97.3 %

Example 184: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-2-methyl-benzoic acid 2-dimethylamino-ethyl ester

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.60

NMR:.$CDCl_3$ ^1H δ (ppm) 2.3 (s,6H) ; 2.55 (s,3H) ; 2.70 (m,2H) ; 3.60 (s, 3H) ; 3.80 (s,3H) ; 4.40 (m,2H) ; 4.60 (m,2H) ; 5.20 (s,2H) ; 6.60 (s,1H) ; 6.80 (m,2H) ; 7.30 (m,5H) ; 7.80 (m,1H) ; 8.30 (m,1H) ; 8.5 (s,1H)

M.P. = 146 °C

HPLC : 99 %

Example 185: 1-Methyl-2,4-dioxo-3-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.30

NMR:.DMSO ^1H δ (ppm) 3.2 (m,1H) ; 3.55 (s, 3H) ; 3.70 (s,3H) ; 4.40 (d,2H) ;5.20 (s,2H) ; 6.90 (m,2H) ; 7.25 (m,2H) ; 7.40 (m,2H) ; 7.55 (m ,1H) ; 7.70 (m,2H) ; 8.30 (m,1H) ; 8.60 (s,1H) ; 9.2 (m,1H)

M.P. = 305 °C

HPLC : 100 %

Example 186: {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-phenyl}-acetic acid

TLC : CH_2Cl_2 / MeOH 90/10 Rf = 0.35

NMR:.DMSO ^1H δ (ppm) 3.50 (m,5H) ; 3.70 (s,3H) ; 4.40 (d,2H) ; 6.80 (d,2H) ; 7.20 (m,4H) ; 7.40 (d,2H) ; 7.60 (d ,1H) ; 8.30 (d,1H) ; 8.60 (s,1H) ; 9.2 (t,1H)

IR = 1717, 1645, 1619, 1501, 1298, 1240, 823, 750

HPLC : 100 %

Example 187: 1-Methyl-3-(1-naphthalen-1-yl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.58

NMR:.DMSO ^1H δ (ppm) 2.0 (d3H) ; 3.45 (s, 3H) ; 4.40 (d,2H) ; 6.00 (s,2H) ; 6.80-6.95 (m,4H) ; 7.4-7.50 (m,3H) ; 7.55 (t,1H) ; 7.85-8.0 (m,4H) ; 8.20 (d,1H) ; 8.6 (s,1H) ; 9.15 (t,1H)

IR : 1656, 1618, 1503, 1440, 1254, 1040, 777, 754 cm^{-1}

M.P. = 157 °C

HPLC : 96.2 %

Example 188 :4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid

To a stirred solution of 0.5 g (0.9 mmol) of the compound obtained in the Example 169 in 50 ml of dichloromethane are added 5 ml of trifluorocetic acid. The mixture is strirred overnight at room temperature and 60 ml of ether are added. The product crystallizes and after filtration 0.44 g (yield: 100%) of the desired compound is obtained.

TLC : CH_2Cl_2 / MeOH 95/5 Rf = 0.60

NMR:.DMSO ^1H δ (ppm): 3.65 (s,3H); 3.75 (s,3H); 4.45 (d,2H); 5.25 (s,2H); 6.90 (d,2H); 7.25 (d,2H); 7.50 (d,2H); 7.90 (d,2H); 8.5 (s,1H); 8.95 (s,1H); 9.20 (t,1H); 12.85 (bs,1H)

IR : 3388, 1715, 1662, 1475, 1442, 1247, 791 cm^{-1}

M.P. = 264.4 °C

HPLC : 98.9 %

Example 189 :3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

To 0.5 g (1.5 mmol) of the compound of Preparation D in dimethylformamide (10 ml) are added EDAC.HCl 0.38g (1.9 mmol), HOBT 0.27 g (1.9 mmol), followed by 4-pyridyl-benzylamine 0.21 g (1.9 mmol). The mixture is stirred 48 hours at room temperature before adding water (20 ml) and extracting with ethyl acetate (2 x 20 ml). The combined organic layers are washed with saturated aqueous NaCl solution (4 x 20 ml), and dried $MgSO_4$. recrystallyzed solid product in hot ethyl acetate to obtain 0.13 g (yield: 20%) of the desired compound.

MS: m/z (APCI, AP+) 419.2 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 66.02; H, 4.58; N, 13.39.
Found (%) : C, 65.73; H, 4.47; N, 13.36.

Example 190: 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

0.10 g (yield: 17%) of the desired compound is obtained according to the procedure of Example 189, but using 2-methoxy-4-pyridyl-benzylamine.

MS: m/z (APCI, AP+) 449.2 $[M^{\cdot}]^+$

CHN Analysis: $C_{24}H_{21}FN_4O_4 \cdot 0.1\ H_2O$

Calcd (%) : C, 64.02; H, 4.75; N, 12.44.

Found (%) : C, 63.66; H, 5.07; N, 12.16.

Example 191: 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

0.11 g (yield : 26%) of the desired compound is obtained according to the procedure of Example 189, but using 3-pyridyl-benzylamine.

MS: m/z (APCI, AP+) 419.1 $[M^{\cdot}]^+$

CHN Analysis: $C_{23}H_{19}FN_4O_3$ 1.2 H_2O

Calcd (%) : C, 62.78; H, 4.90; N, 12.73.

Found (%) : C, 62.75; H, 4.90; N, 12.73.

Example 192: 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

0.12 g (yield: 35%) of the desired compound is obtained according to the procedure of Example 189, but using 4-methoxy-benzylamine.

MS: m/z (APCI, AP+) 448.1 $[M^{\cdot}]^+$

CHN Analysis: $C_{25}H_{22}FN_3O_4 \cdot 0.1\ H_2O$

Calcd (%) : C, 66.84; H, 4.98; N, 9.35.

Found (%) : C, 66.57; H, 4.83; N, 9.03.

Example 193: 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide

0.20 g (yield : 59%) of the desired compound is obtained according to the procedure of Example 189, but using 3-methoxy-benzylamine.

MS: m/z (APCI, AP+) 448.1 $[M^{\cdot}]^+$

CHN Analysis: $C_{25}H_{22}FN_3O_4$

Calcd (%) : C, 67.11; H, 4.96; N, 9.39.

Found (%) : C, 66.82; H, 4.87; N, 9.11.

Example 194 :1-Ethyl-3-(3-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

0.13 g (yield : 20%) of the desired compound is obtained according to the procedure of Example 189, but using the compound of the Preparation E and 4-pyridyl-benzylamine.

MS: m/z (APCI, AP+) 433.2 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 66.66; H, 4.89; N, 12.96.

Found (%) : C, 66.26; H, 4.71; N, 12.78.

Example 195: 1-Ethyl-3-(3-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

0.18 g (yield : 51%) of the desired compound is obtained according to the procedure of Example 189, but using the compound of Preparation E and 3-pyridyl-benzylamine.

MS: m/z (APCI, AP+) 433.1 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 66.66; H, 4.89; N, 12.96.

Found (%) : C, 66.43; H, 5.03; N, 12.84.

Example 196: 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

Step 1: Methyl 3-(4-bromobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

4.6 g (yield : 59%) of the desired compound is obtained according to the procedure of Step 1 of Preparation D, but using 4-bromobenzyl isocyanate.

MS: m/z (APCI, AP+) 388.9 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 52.46; H, 3.37; N, 7.20.

Found (%) : C, 52.16; H, 3.30; N, 7.30.

Step 2: Methyl 1-methyl-3-(4-bromobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

1.49 g (yield : 71%) of the desired compound is obtained according to the procedure of step 2 of Preparation D, but using the compound obtained in the Preceding Step 1.

MS: m/z (APCI, AP+) 404.9 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 53.62; H, 3.75; N, 6.95.

Found (%) : C, 53.24; H, 3.71; N, 6.84.

Step 3: 1-Methyl-3-(4-bromobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

1.3 g (yield : 87%) of the desired compound is obtained according to the procedure of Step 2-4 of Preparation B, but using the compound obtained in the preceding Step 2.

MS: m/z (APCI, AP+) 388.9 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 52.46; H, 3.37; N, 7.20.

Found (%) : C, 52.12; H, 3.30; N, 7.11.

Step 4: 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

0.24 g (yield : 76%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the preceding Step 3 and 4-methoxy-benzylamine.

MS: m/z (APCI, AP+) 508 $[M^{\cdot}]^+$

CHN Analysis: $C_{25}H_{22}BrN_3O_4$ 0.2 H_2O

Calcd (%) : C, 58.65; H, 4.41; N, 8.21.

Found (%) : C, 58.32; H, 4.32; N, 8.12.

Example 197: 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

0.22 g (yield : 33%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the preceding Step 3 and 2-methoxy-4-pyridyl-benzylamine.

NMR: DMSO ^1H δ (ppm): 3.52 (3H,s); 3.79 (3H,s); 4.43 (2H,d); 5.09 (2H,s); 6.66 (1H,s); 6.89 (1H,d); 7.26-7.56 (5H,m); 8.06 (1H,d); 8.24-8.26 (1H,m); 8.61(1H,m); 9.31 (1H,t).

MS: m/z (APCI, AP+) 509 $[M^{\cdot}]^+$

Example 198: 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

Step 1: Methyl 3-(3,4-difluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

The compound is obtained with 51% yield according to the procedure of Step 1-5 to Step 2-5 of Preparation B using as substrates the compound of Preparation A and 3,4-difluorobenzylamine.

NMR: DMSO ^{1}H (ppm): 3.86 (3H,s); 5.05 (2H,s); 6.66 (1H,s); 7.18-7.43 (4H,m); 8.18 (1H,dd); 8.47 (1H,s).

MS: m/z (APCI, AP+) 347.1 $[M^{\cdot}]^+$

Step 2 : Methyl 1-methyl-3-(3,4-difluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

1.5 g (yield : 72%) of the desired compound is obtained according to the procedure of Step 2 of the Preparation D, but using the compound obtained in the preceding Step 1.

MS: m/z (APCI, AP+) 361.0 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 60.00; H, 3.92; N, 7.77.
Found (%) : C, 60.05; H, 3.85; N, 7.72.

Step 3: 1-Methyl-3-(3,4-difluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

1.1 g (yield : 82%) of the desired compound is obtained according to the procedure of Step 2-4 of the Preparation B, but using the compound obtained in the preceding Step 2.

MS: m/z (APCI, AP+) 437.0 $[M^{\cdot}]^+$

CHN Analysis: Calcd (%) : C, 58.96; H, 3.49; N, 8.09.
Found (%) : C, 58.67; H, 3.99; N, 7.27.

Step 4: 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

0.48 g (yield : 79%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the preceding Step 3 and 3-pyridyl-benzylamine.

MS: m/z (APCI, AP+) 437.1 $[M^{\cdot}]^+$

CHN Analysis: $C_{23}H_{18}F_2N_4O_3$ 0.2 H_2O

Calcd (%) : C, 62.78; H, 4.21; N, 12.73.

Found (%) : C, 62.50; H, 4.13; N, 12.82.

Example 199 :3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

0.23 g (yield : 38%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the Step 3 of the Example 198 and 4-pyridyl-benzylamine.

MS: m/z (APCI, AP+) 437.1 $[M^{\cdot}]^+$

CHN Analysis: $C_{23}H_{18}F_2N_4O_3$

Calcd (%) : C, 63.30; H, 4.16; N, 12.84.

Found (%) : C, 63.19; H, 4.07; N, 12.81.

Example 200 :3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

0.11 g (yield : 39%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the Step 3 of the Example 198 and 4-methoxy-benzylamine.

MS: m/z (APCI, AP+) 466.2 $[M^{\cdot}]^+$

CHN Analysis: $C_{25}H_{21}F_2N_3O_4$

Calcd (%) : C, 64.51; H, 4.55; N, 9.03.

Found (%) : C, 64.41; H, 4.53; N, 8.87.

Example 201: 3-(3-chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

Step 1: Methyl 3-(3-chloro-4-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

The compound is obtained with 18.1% yield according to the procedure of Step 1-5 to Step 2-5 of Preparation B using as substrates the compound of Preparation A and 3-chloro-4-fluorobenzylamine.

MS: m/z (APCI, AP$^-$) 361.0 $[M^-]^+$

Step 2 : Methyl 1-methyl-3-(3-chloro-4-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

0.5 g (yield : 72%) of the desired compound is obtained according to the procedure of Step 2 of the Preparation D, but using the compound obtained in the preceding Step 1.

MS: m/z (APCI, AP+) 377.0 $[M^-]^+$

CHN Analysis: Calcd (%) : C, 57.38; H, 3.75; N, 7.44.
Found (%) : C, 57.34; H, 3.73; N, 7.27.

Step 3: 1-Methyl-3-(3-chloro-4-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

0.45 g (yield : 92%) of the desired compound is obtained according to the procedure of Step 2-4 of the Preparation B, but using the compound obtained in the preceding Step 2.

MS: m/z (APCI, AP+) 363.0 $[M^-]^+$

CHN Analysis: Calcd (%) : C, 56.29; H, 3.33; N, 7.72.
Found (%) : C, 56.24; H, 3.21; N, 7.64.

Step 4: 3-(3-chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

0.17 g (yield : 69%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the preceding Step 3 and 4-pyridyl-benzylamine.

MS: m/z (APCI, AP+) 453.1 $[M^-]^+$

CHN Analysis: $C_{23}H_{18}F_2N_4O_3 \cdot 1.1\ H_2O$
Calcd (%) : C, 58.44; H, 4.31; N, 11.85.
Found (%) : C, 58.23; H, 4.23; N, 11.75.

Example 202 :3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

0.21 g (yield : 80%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the Step 3 of the Example 201 and 4-methoxy-benzylamine.

MS: m/z (APCI, AP+) 482.1 $[M^{\cdot}]^{+}$

CHN Analysis: $C_{25}H_{21}ClFN_3O_4$

Calcd (%) : C, 62.31; H, 4.39; N, 8.72.

Found (%) : C, 62.12; H, 4.37; N, 8.51.

Example 203 :4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate(2-hydroxy-ethyl)-trimethyl-ammonium

A suspension of 0.5 g (1.05 mmol) of compound of the Example 34 in hot methanol is added 0.22g (1.03 mmol) choline bicarbonate. The mixture is heated to reflux for 1 hour. Cool and concentrate. The resulting solid is recrystallized from ethanol to provide 0.41 g (yield: 68%) of the desired compound.

CHN Analysis: $C_{31}H_{36}N_4O_7 \cdot 0.5\ H_2O$

Calcd (%) : C, 63.58; H, 6.37; N, 9.57.

Found (%) : C, 63.32; H, 6.58; N, 9.57.

Example 204: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid hemicalcium salt

A suspension of 0.5 g (1.05 mmol) of compound of the Example 34 in warm tetrahydrofuran is added 1.05 ml 1.00 N NaOH. The mixture is stirred 0.5 hour and $CaCl_2$ 0.058 g (0.525 mmol) is added in one portion. The mixture is stirred 2 hours and then concentrated. Add ethanol and filter. Dried at 88°C in vacuum oven for 72 hours gives 0.49 g (yield : 94%) of the desired compound.

CHN Analysis: $C_{52}H_{44}CaN_6O_{12} \cdot 1.0\ H_2O$

Calcd (%) : C, 62.27; H, 4.62; N, 8.38.

Found (%) : C, 61.95; H, 4.70; N, 8.34.

Example 205 :4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid hemimagnesium salt

A suspension of 0.5 g (1.05 mmol) of compound of the Example 34 in warm tetrahydrofuran is added 1.05 ml 1.00 N NaOH. The mixture is stirred 0.5 hour and $MgCl_2$ 0.052 g (0.525 mmol) is added in one portion. The mixture is stirred 2 hours and then concentrated. Add ethanol and filter. Dried at 88°C in vacuum oven for 72 hours gives 049 g (yield : 96%) of the desired compound.

CHN Analysis: $C_{52}H_{44}MgN_6O_{12} \cdot 1.0\ H_2O$

Calcd (%) : C, 63.26; H, 4.70; N, 8.51.

Found (%) : C, 63.07; H, 4.89; N, 8.50.

Example 206: 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridazin-4-ylmethyl)-amide

To a suspension of compound of the Step 1 of the Example 33 (1.00 g, 4.54 mmol), EDAC (1.13 g, 5.90 mmol), HOBT (0.675 g, 5.00 mmol) in 20 ml of DMF is added a solution of 4-aminomethyl-pyridine (0.507 ml, 5.00 mmol). The light orange suspension is stirred at room temperature overnight. After 24 h, the reaction mixture is concentrated affording a offwhite solid. The solids are subsequently washed with 10 ml of ethyl acetate, saturated Na_2CO_3, and 10 ml of H_2O to give 1.20 g (yield: 85.7%) of product.

MP: 141-145 °C

MS(APCI+): m/z 309.1 (MH^+).

Step 2: 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

To a suspension of compound obtained in the preceding Step 1 (0.200 g, 0.645 mmol) in 6 ml of DMF is added Cs_2CO_3 (0.630 g, 1.93 mmol). After stirring at room temperature for 30 min, a solution of 4-chlorobenzyl-bromide (0.132 g, 0.645 mmol) in 2 ml of DMF is added dropwise to the reaction mixture and stirred overnight. White solids (cesium salt) are filtered and the solution was concentrated. The resulting suspension is diluted with 10 ml of ethyl acetate and filtered again. The filtrate is concentrated and tritutration with 10 ml of ethyl acetate gave 0.26 g (yield: 92.9%) of a white solid corresponding to the desired compound.

MP: 228-230 °C

CHN Analysis: $C_{23}H_{19}N_4O_3Cl_1$

Calcd (%) : C, 63.52; H, 4.40; N, 12.88.

Found (%) : C, 63.40; H, 4.41; N, 12.84.

Example 207: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

0.2 g of the desired compound (yield: 74.1%) is obtained according to the procedure of Example 206, Steps 1 to 2, but using in Step 2 4-fluorobenzyl bromide.

mp 210-212 °C;

CHN Analysis: $C_{23}H_{19}N_4O_3F_1$

Calcd (%) : C, 66.02; H, 4.58; N, 13.39

Found (%) : C, 65.74; H, 4.60; N, 13.03.

Example 208: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

1.18 g of the desired compound (yield: 83.7%) is obtained according to the procedure of Step 1 of the Example 206, but using 3-aminomethyl pyridine.

MS(APCI+): m/z 309.1 (MH^+);

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.43 (s, 3H, NCH_3), 4.47 (d, J=5.86 Hz, 2H, NCH_2Ar), 7.31-7.34 (m, 1H, ArH), 7.48 (d, J=8.79 Hz, 1H, ArH), 7.70 (d, J=7.82 Hz, 1H, ArH), 8.20 (dd, J=8.79, 1.95 Hz, 1H, ArH), 8.42-8.43 (m, 1H, ArH), 8.53 (d, J=2.20 Hz, 2H, ArH), 9.30 (t, J=5.62, 1H, ArH), 11.65 (s, 1H, NH);

Step 2: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

0.25 g of the desired compound (yield: 82.6%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in the preceding Step 1 and 4-fluorobenzyl bromide.

MP : 166-168 °C

Anal. Calcd for $C_{23}H_{19}N_4O_3F_1$: C, 65.79; H, 4.60; N, 13.34. Found: C, 65.40; H, 4.40; N, 13.18.

Example 209: 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

0.25 g of the desired compound (yield: 89.3%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in the Step 1 of Example 208 and 4-chlorobenzyl bromide.

MP : 173-175 °C

Anal. (%) Calcd for $C_{23}H_{19}N_4O_3Cl_1$: C, 62.77; H, 4.48; N, 12.73. Found: C, 62.39; H, 4.46; N, 12.71.

Example 210: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide

Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide

1.29 g of the desired compound (yield: 83.8%) is obtained according to the procedure of Example 206, Step 1, but using 3-methoxylbenzyl amine.

MP: 235-238°C.

Step 2: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide

0.25 g of the desired compound (yield: 95%) is obtained according to the procedure of Example 206, Steps 2, but using the compound obtained in the preceding Step 1 and 4-fluorobenzyl bromide.

MP : 176-178°C

Anal. (%) Calcd for $C_{25}H_{22}N_3O_4F_1$: C, 67.11; H, 4.96; N, 9.39. Found: C, 66.99; H, 4.99; N, 9.18.

Example 211: 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide

0.25 g of the desired compound (yield: 92%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in the Step 1 of Example 210 and 4-chlorobenzyl bromide.

MP: 178-180 °C

Anal. (%) Calcd for $C_{25}H_{22}N_3O_4Cl_1$: C, 64.60; H, 4.79; N, 9.04. Found: C, 64.22; H, 4.72; N, 8.84.

Example 212: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

Step 1: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

1.00 g of the desired compound (yield: 76.9%) is obtained according to the procedure of Example 206, Step 1, but using (2-methoxy-pyridin-4-yl)-methylamine.

MP: 215-218 °C

MS(APCI+): m/z 339.1 (MH^+).

Step 2: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

0.07 g of the desired compound (yield: 26.5%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in the preceding Step 1 and 4-fluorobenzyl bromide.

MP : 174-175 °C

Anal. (%) Calcd for $C_{24}H_{21}N_4O_4F_1$: C, 64.20; H, 4.73; N, 12.48. Found: C, 63.88; H, 4.73; N, 12.08.

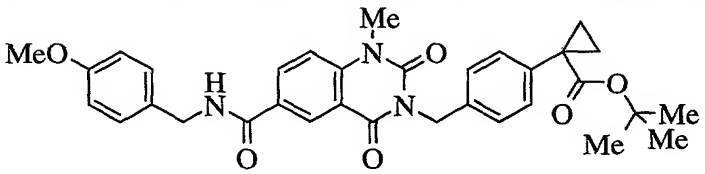
Example 213: 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

0.09 g of the desired compound (yield: 33%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in Step 1 of Example 212 and 4-chlorobenzyl bromide.

MP :169-170 °C

Anal. (%) Calcd for $C_{24}H_{21}N_4O_4Cl_1$: C, 62.02; H, 4.61; N, 11.98. Found: C, 62.01; H, 5.01; N, 11.70.

Example 214: tert-Butyl 1-{4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylate



0.35 g of the desired compound (yield: 67%) is obtained according to the procedure of Example 206, Steps 1 to 2, but using in Step 1 4-methoxy-benzylamine and in Step 2 *tert*-butyl 1-(4-bromomethyl-phenyl)-cyclopropanecarboxylate.

MP: 148-149 °C

Anal. (%) Calcd for $C_{33}H_{35}N_3O_6$: C, 68.88; H, 6.24; N, 7.30. Found: C, 68.49; H, 6.29; N, 7.21.

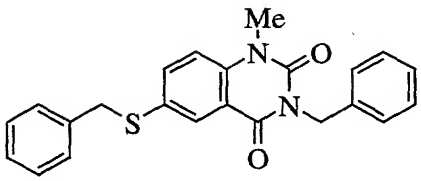
Example 215: 1-{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid

To a solution of the compound of Example 214 (0.35 g, 0.61 mmol) in 2 ml of CH_2Cl_2 are added 2 ml of TFA. The yellow solution is stirred at room temperature for 4 hours. The reaction mixture is concentrated and trituration with diethyl ether gives 0.25 g (yield:79%) of a white solid corresponding to the desired compound.

MP : 179-181°C

Anal. (%) Calcd for $C_{29}H_{27}N_3O_6$: C, 66.22; H, 5.35; N, 7.77. Found: C, 66.61; H, 5.40; N, 8.04.

Example 216: 3-Benzyl-6-benzylsulfanyl-1-methyl-1H-quinazoline-2,4-dione



Step 1: 5-Iodo-2-methylamino-benzoic acid

To a solution of N-methylanthranilic acid (5.00 g, 3.31 mmol) in 30 ml of acetic acid are added 60 ml of H_2O and I_2 (8.39 g, 3.31 mmol) is added portionwise over a period of 5 minutes. The reaction mixture is stirred at room temperature for 2 days. After 48 hours, the product is filtered and washed with 30 ml of H_2O. The mother liquor is concentrated affording more product

Weight: 7.3 g; **Yield** = 80%

MP: 170-172 °C

MS(APCI+): m/z 276.0 (MH^+).

Step 2: 3-Benzyl-6-iodo-1-methyl-1*H*-quinazoline-2,4-dione

To a mixture of the compound obtained in the preceding Step 1 (0.50 g, 1.9 mmol), isothiocyanate (0.236 g, 1.58 mmol), and CF_3CO_2Ag (0.838 g, 3.80 mmol) is added slowly Et_3N. The reaction mixture is heated at refluxed for 1.5 hours. After cooled to room temperature, silver sulfide is filtered and the filtrate is concentrated affording a brown oil. The product is purified by chromatography on silica gel (ethyl acetate/hexane: 20/80) to give 0.300 g (48.0%) of a white solid

MP: 149-150°C

MS(APCI+): m/z 391.0 (MH^+).

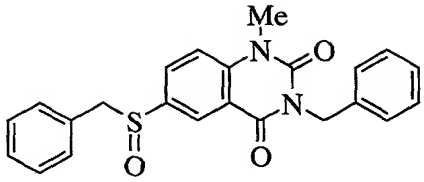
Step 3: 3-Benzyl-6-benzylsulfanyl-1-methyl-1*H*-quinazoline-2,4-dione

To a mixture of $KHCO_3$ (0.009 g, 0.089 mmol), PPh_3 (0.007 g, 0.027 mmol), n-Bu_4NI (0.033 g, 0.089 mmol), $Pd(OAc)_2$ (0.002 g, 0.009 mmol), after purging with N_2 for 5 min, are added a solution of the compound of the preceding Step 2 (0.035 g, 0.089 mmol) and butyl-thiocarbamic acid S-benzyl ester (0.020 g, 0.089 mmol) in 5 ml of dioxane at room temperature. The brown solution is heated at 100°C for overnight. After 24 hours, the reaction mixture is cooled to room temperature and diluted with 20 ml of ethyl acetate, filtered through a sheet of celite, washed with H_2O (2x5 ml), concentrated affording a yellow oil. Tritutration with diethyl gives 0.025 g (yield: 72%) of a yellow solid corresponding to the desired compound.

MP: 117-118°C

Anal. (%) Calcd for $C_{23}H_{20}N_2O_2S_1$: C, 69.66; H, 5.31; N, 7.06. Found: C, 69.26; H, 5.04; N, 6.93.

Example 217: 3-Benzyl-1-methyl-6-phenylmethanesulfinyl-1*H*-quinazoline-2,4-dione



To a solution of the compound of Example 216 (0.050 g, 0.129 mmol) in 9 ml of anhydrous CH_2Cl_2 is added *m*-chloro-perbenzoic acid (0.029 g, 0.127 mmol) at -5°C. After stirring at -5°C for 3 hours, the reaction mixture is quenched with 20 ml of $NaHCO_3$ while in the ice-bath. The organic layer is separated and the aqueous is extracted with CH_2Cl_2 (2x20 ml). The combined organic layers concentrated affording a yellow oil. The product is purified by chromatography on silica gel (ethyl acetate/hexane: 30/70) to give 0.070 g (yield: 33.7%) of a white solid corresponding to the desired compound.

MP: 182-183°C

Anal. (%) Calcd for $C_{23}H_{20}N_2O_3S_1$: C, 67.84; H, 5.03; N, 6.88. Found: C, 68.13; H, 4.86; N, 6.48.

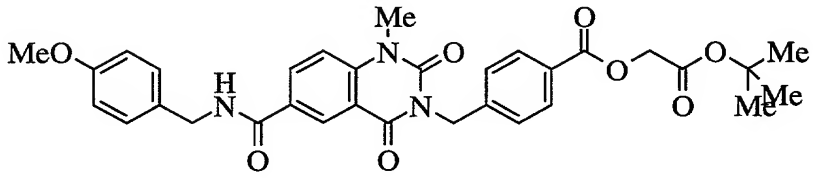
Example 218 :3-Benzyl-1-methyl-6-phenylmethanesulfonyl-1*H*-quinazoline-2,4-dione

To a solution of the compound of Example 216 (0.133 g, 0.342 mmol) in 25 ml of anhydrous CH_2Cl_2 is added *m*-chloro-perbenzoic acid (0.153 g, 0.685 mmol) at -5°C. After stirring at -5 °C for 5 min, the ice-bath is removed and the reaction mixture is stirred at room temperature for 3 hours. The reaction is completed and quenched with 5 ml of saturated $NaHCO_3$. The organic layer is separated and the aqueous is extracted with CH_2Cl_2 (2x20 ml). The combined organic layers concentrated affording a yellow oil. Tritutration with ethyl acetate gives 0.80 g (yield: 56%) of a light yellow solid corresponding to the desired compound.

MP : 173-175°C

Anal. (%) Calcd for $C_{23}H_{20}N_2O_4S_1$: C, 64.73; H, 4.89; N, 6.56. Found: C, 64.34; H, 4.72; N, 6.18.

Example 219: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid tert-butoxycarbonylmethyl ester

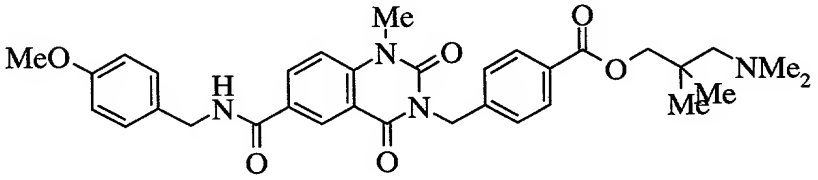


To 0.40 g (0.84 mmol) of the compound of Example 35 in dimethylformamide (10 ml) is added di-isopropylethylamine 0.13g (1.0mmol) followed by tert-butylacetyl chloride 0.18 g (1.18 mmol). The mixture is stirred overnight at room temperature before concentrating in-vacuo, then diluted with ethyl acetate (20 ml). The organic layer is washed with saturated aqueous NaCl solution (2x20 ml), dried $MgSO_4$; and purified by flash chromatography (EtOAC/ hexane eluent) to give 0.11 g (yield: 23%) of the desired compound.

MS: m/z (APCI, AP+) 588.4 $[M^{\cdot}]^+$

CHN Analysis (%) : $C_{32}H_{33}N_3O_8 \cdot 1.8\ H_2O$ Calcd: C, 61.97; H, 5.61; N, 6.70. Found: C, 61.58; H, 5.61; N, 6.70.

Example 220: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid dimethylamino-dimethyl-propyl ester

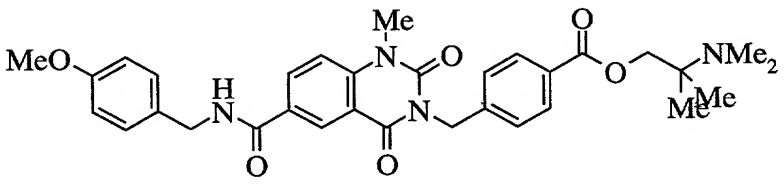


To 0.50 g (1.6 mmol) of compound of Example 35 in dimethylformamide (20 ml) is added EDAC HCl 0.39g (2.1 mmol), HOBT 0.28 g (2.1 mmol), followed by dimethylamino-dimethyl-propan-1-ol 0.27 g (2.1 mmol). The mixture is stirred overnight at room temperature before adding water (20 ml) and extracting with ethyl acetate (2 x 20 ml). The combined organic layers are washed with saturated aqueous NaCl solution (4 x 20 ml), and dried MgSO4. The crude product is dissolved in EtOAc/MeOH and saturated ethereal HCl. is added. After concentration and solidification in EtOAc, 0.49 g (yield: 43%) of the desired compound is obtained.

MS: m/z (APCI, AP+) 587.0 $[M^{\cdot}]^+$

CHN Analysis (%): $C_{33}H_{38}N_4O_6$ 1.0 HCl $\cdot$ 1.2 H_2O Calcd: C, 61.40; H, 6.48; N, 8.68. Found: C, 61.01; H, 6.31; N, 8.99.

Example 221: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid dimethylamino-methyl-propyl ester



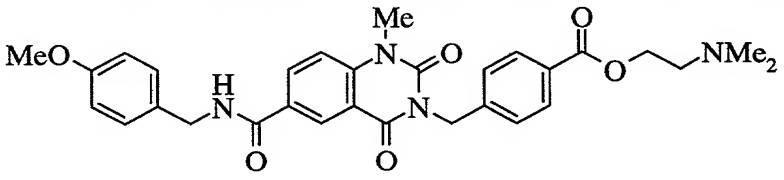
To 0.50 g (1.6 mmol) of the compound of Example 35 in dimethylformamide (20 ml) is added EDAC HCl 0.39g (2.1 mmol), HOBT 0.28 g (2.1 mmol), followed by

dimethylamino-methyl-propan-1-ol 0.24 g (2.1 mmol). The mixture is stirred overnight at room temperature before adding water (20 ml) and extracting with ethyl acetate (2x20 ml). The combined organic layers are washed with saturated aqueous NaCl solution (4 x 20 ml), and dried $MgSO_4$. The crude product is dissolved in EtOAc/MeOH and saturated ethereal HCl. is added. After concentration and solidification in EtOAc, 0.21 g (yield: 21%) of the desired compound is obtained.

MS: m/z (APCI, AP+) 573.2 $[M^{\cdot}]^+$

CHN Analysis (%): $C_{32}H_{36}N_4O_6$ 1.0 HCl · 0.48 H_2O Calcd: C, 62.22; H, 6.19; N, 9.07. Found: C, 61.82; H, 6.00; N, 9.16.

Example 222: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid 2-dimethylamino-ethyl ester

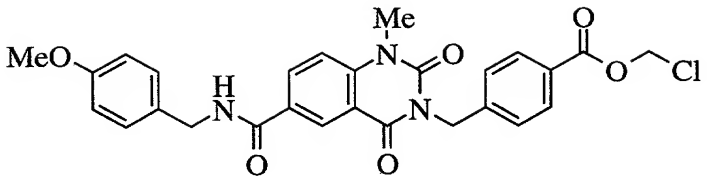


To 0.73 g (1.5 mmol) of the compound of Example 35 in dimethylformamide (10 ml) is added EDAC HCl 0.38g (2.0 mmol), HOBT 0.27 g (2.0 mmol), followed by dimethylamino-propan-1-ol 0.18 g (2.0 mmol). The mixture is stirred overnight at room temperature before adding water (20 ml) and extracting with ethyl acetate (2 x 20 ml). The combined organic layers are washed with saturated aqueous NaCl solution (2 x 20 ml), and dried $MgSO_4$. the crude product is solidified in EtOAc to give 0.49 g (yield: 60%) of the desired compound.

MS: m/z (APCI, AP+) 545.3 $[M^{\cdot}]^+$

CHN Analysis (%): $C_{30}H_{32}N_4O_6$ 0.25 H_2O Calcd: C, 65.62; H, 5.97; N, 10.20. Found: C, 65.62; H, 5.92; N, 10.23.

Example 223: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid chloromethyl ester

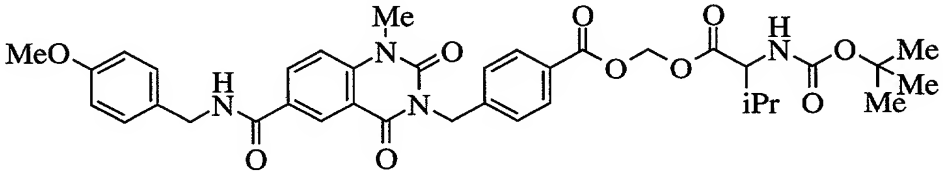


To 1.0 g (2.1 mmol) of the compound of Example 35 in dimethylformamide (15 ml) is di-isopropylethylamine 0.47g (3.6 mmol) followed by chloro-iodomethane 1.86 g (10.5 mmol). The mixture is stirred overnight at room temperature before diluting with ethyl acetate (20 ml). The organic layer is washed with water (1x10 ml) saturated aqueous NaCl solution (2x10 ml), and dried $MgSO_4$. After solidification in ether 0.29 g (yield: 26%) of the desired compound is obtained.

MS: m/z (APCI, AP+) 522.2 $[M^{\cdot}]^+$

CHN Analysis (%): $C_{27}H_{24}ClN_3O_6$ Calcd: C, 62.13; H, 4.63; N, 8.05. Found: C, 62.08; H, 4.61; N, 7.95.

Example 224: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-tert-butoxycarbonylamino-3-methyl-1-butanoyloxymethyl ester ester

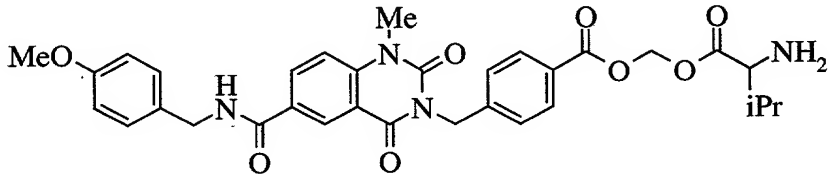


To 0.39 g (0.75 mmol) of the compound of Example 223 in dimethylformamide (10 ml) is added di-isopropylethylamine 0.12g (0.96 mmol) followed by t-butoxycarbonyl-leucine 0.21 g (0.96 mmol). The mixture is stirred overnight at 60-70C for 12 hours, cooled and diluted with ethyl acetate (20 ml). The organic layer is washed with water (1 x 10 ml), 5% aqueous $NaHCO_3$ solution (1x10 ml), saturated aqueous NaCl (1x10 ml), dried $MgSO_4$, and purified by flash chromatography (EtOAC/ hexane eluent) to give 0.14 g (yield: 25%) of the desired compound.

MS: m/z (APCI, AP+) 701.3 $[M^{\cdot} - Boc]^-$

CHN Analysis (%): $C_{37}H_{42}N_4O_{10}$ Calcd: C, 61.97; H, 5.61; N, 6.70. Found: C, 61.58; H, 5.61; N, 6.70.

Example 225: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid 2-amino-3-methyl-butanoyloxymethyl ester hydrochloride

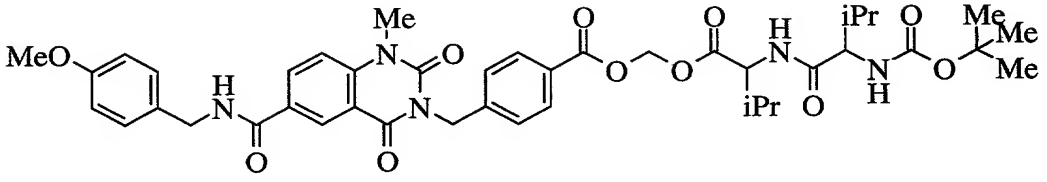


To 0.14 g (0.19 mmol) of the compound of Example 224 in dioxane (10 ml) is added 1.0 M HCl in ether (10 ml). HCl gas is bubbled through for 2 minutes then mixture is stirred 90 minutes at room temperature. After concentration and trituration in EtOAc, 0.039 g (yield: 30%) of the desired compound is obtained.

MS: m/z (APCI, AP+) 603.2 $[M^{\cdot}]^{+}$

CHN Analysis (%): $C_{37}H_{42}N_4O_{10}$ Calcd: C, 61.97; H, 5.61; N, 6.70. Found: C, 61.58; H, 5.61; N, 6.70.

Example 226: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-(2-tert-butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester



Step 1: 2-(2-tert-Butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butyric acid methyl ester

To 1.3 g (5.9 mmol) of t-butoxycarbonyl-leucine in dimethylformamide (15 ml) is added EDAC HCl 1.4g (7.1 mmol), HOBT 0.95 g (7.1 mmol), followed by NH_2-Leu-OMe 1.0 g (5.9 mmol). The mixture is stirred overnight at room temperature before adding water (20 ml) and extracting with ethyl acetate (2 x 20 ml). The combined organic layers are washed

with 10% aqueous Na_2CO_3 (1 x 10 ml), saturated aqueous NaCl solution (2 x 20 ml), and dried $MgSO_4$. A solidification in ether gives 1.05 g (yield: 53%) of the desired compound.

MS: m/z (APCI, AP+) 331.2 $[M^-]^+$

CHN Analysis (%): $C_{16}H_{30}N_2O_5$ Calcd: C, 58.16; H, 9.15; N, 8.48. Found: C, 58.32; H, 9.24; N, 8.51.

Step 2: 2-(2-tert-Butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butyric acid

To 0.4 g (1.2 mmol) of the compound obtained in the preceding step 1, in 3:1:1 methanol/water/THF (10 ml) is added LiOH H_2O, 0.06 g (1.44 mmol). The mixture is stirred overnight at room temperature. Partitioned between water (20 ml) and ethyl acetate (30 ml). The layers are separated and the aqueous layer made acidic with 2 M HCl. The product is extracted with EtOAc (2 x 20 ml) washed with saturated aqueous NaCl solution (1 x 20 ml), and dried $MgSO_4$. A solidification in ether gives 0.22 g (yield: 58%) of the desired compound.

MS: m/z (APCI, AP+) 317.2 $[M^-]^+$

CHN Analysis (%): $C_{15}H_{28}N_2O_5$ Calcd: C, 56.94; H, 8.92; N, 8.85. Found: C, 56.72; H, 8.89; N; 8.64

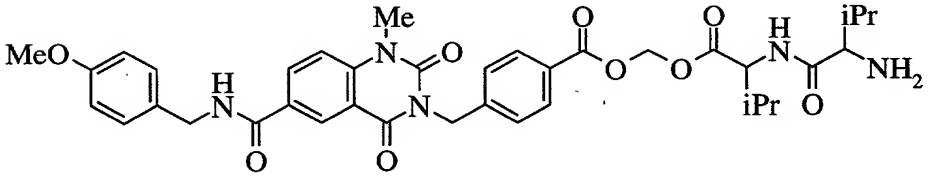
Step 3: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid 2-(2-tert-butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester

To 0.29 g (0.56 mmol) of the compound obtained in Example 223 in dimethylformamide (10 ml) is added di-isopropylethylamine 0.092g (0.72 mmol) followed by compound obtained in the preceding Step 2, 0.23 g (0.72 mmol) then NaI (cat.). The mixture is stirred overnight at 50°C for 18 hours. Cool and dilute with water and extract with ethyl acetate (2 x 20 ml). The combined organic layer are washed with saturated aqueous $NaHCO_3$ solution (1 x 10 ml), saturated aqueous NaCl (3 x 10 ml) and dried $MgSO_4$. a solidification in a mixture of EtOAc/hexane gives 0.27 g (yield: 63%) of the desired compound.

MS: m/z (APCI, AP+) 800.4 $[M^- - Boc]^-$

CHN Analysis (%): $C_{37}H_{42}N_4O_{10}$ Calcd: C, 62.91; H, 6.41; N, 8.73. Found: C, 62.59; H, 6.44; N, 8.39.

Example 227: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid 2-(2-amino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester



To 0.25 g (0.31 mmol) of compound of the Example 226 in dioxane (10 ml) is added 1.0 M HCl in ether (10 ml). HCl gas is bubbled through for 2 minutes then mixture is stirred 90 minutes at room temperature. After concentration and trituration in EtOAc, 0.12 g (yield: 55%) of the desired compound is obtained.

MS: m/z (APCI, AP+) 702.0 $[M^{\cdot}]^+$

CHN Analysis (%): $C_{37}H_{43}N_5O_9$ Calcd: C, 63.33; H, 6.18; N, 9.98. Found: C, 62.99; H, 6.06; N; 9.72.

Examples 228 to 345:

These compounds were obtained according to the procedure described in the Example 168 followed by the procedure of the Example 169.

3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,

3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

and 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d] pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide.

Examples 345 to 461:

These compounds were obtained according to the procedure described for Example 131:

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

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3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

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3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

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3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,

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3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

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3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

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3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

and 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide.

EXAMPLE 462

Evaluation of the *in vitro* activity of the compounds of formula (I) according to the invention.

The ability of the compounds of formula (I) of the invention to inhibit matrix metalloprotease 13 was evaluated by measuring their IC_{50} value (concentration required to inhibit 50% of the enzymatic activity) according to the protocol described below.

MMP13CD Thiopeptolide Assay: Proteolysis of the thiopeptolide substrate Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OEt is used as the primary screen to determine IC_{50} values for MMP13 inhibitors. A 100 µl reaction contains 50 mM HEPES, 10 mM $CaCl_2$, pH 7.0 (RT), 1 mM 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), 100 µM substrate, inhibitor in 2.0% DMSO and 2.5 nM human collagenase-3 catalytic domain enzyme. Inhibitors are screened from 100 µM to 0.5 nM. The change in absorbance at 405 nm is monitored on a microplate reader at room temperature continuously for 10-15 minutes. Percentage of control velocity in inhibited treatments is plotted against inhibitor concentration to calculate IC_{50} values.

Table 1

Example	IC_{50} (µM)	Example	IC_{50} (µM)
5	0.193	30	0.009

6	0.183	31	1.7
7	0.021	32	0.017
8	1.87	33	0.003
9	0.366	34	0.026
10	0.049	35	0.157
11	0.167	36	0.6
12	1.32	37	0.75
13	0.005	38b	0.004
14	0.057	39	0.001
15	2.25	40	0.028
16	0.042	41	0.029
17	0.012	42	0.031
18	0.051	43	0.011
19d	0.7	44	0.004
20	0.015	45	0.007
21	0.009	46	0.0025
22b	0.01	47	1.21
24	0.051	48	0.016
25	0.3	49	0.007
26	0.096	50	0.096
27	0.029	51	0.062
28	0.009	52	0.014
29	0.028		

Examination of the results of Table 1 shows that the products of the invention tested in the assay effectively inhibit matrix metalloprotease 13.

The protocol described above was also used to measure the activity of the compounds of the invention against MMP1, MMP2, MMP3, MMP7, MMP9, MMP12 and MMP14. The IC_{50} values obtained on these MMPs were often greater than 100 μM. These results indicate that the compounds of the invention are selective MMP13 inhibitors.

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